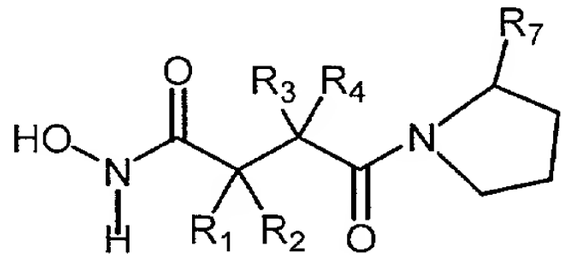
4-fluorophenylaminocarbonyl, *N*-methyl-*N*-phenylaminocarbonyl, 2-propylaminocarbonyl, 2-phenylpropylaminocarbonyl, *n*-propylaminocarbonyl, *N*-ethyl-*N*-(*n*-butyl)aminocarbonyl, benzylaminocarbonyl, thiazolidin-1-ylcarbonyl, pyrimidin-2-ylaminocarbonyl, 4-methylpyrimidin-2-ylaminocarbonyl, pyrimidin-4-yl-aminocarbonyl, pyrazin-2-ylaminocarbonyl, imidazol-2-ylaminocarbonyl.

In particular, R_7 is ethylaminocarbonyl, phenylaminocarbonyl, pyrimidin-2-ylaminocarbonyl, or thiazol-2-ylaminocarbonyl. More particularly, R_7 is phenylaminocarbonyl or pyrimidin-2-ylaminocarbonyl. The stereochemistry at the C2 carbon atom of the pyrrolidine ring, i.e., carbon carrying the R_7 group is either (*R*) or (*S*), preferably (*S*); or

(b) $-NHC(=O)OR_{14}$ where R_{14} is hydrogen, $-(C_1-C_{12})$ alkyl, substituted alkyl, or heteroalkyl, $-(C_1-C_{12})$ alkenyl, substituted alkenyl, or heteroalkenyl, $-(C_1-C_{12})$ alkynyl, substituted alkynyl, or heteroalkynyl, alkoxy, or $-(C_1-C_8$ alkyl or substituted alkyl$)_{n9}-(C_3-C_{12}$ arylene or heteroarylene$)-(C_1-C_8$ alkyl or substituted alkyl$)_{n10}$ where n9 and n10 are independently 0 or 1. Preferably, R_7 is $-NHC(=O)OR_{14}$ where R_{14} is hydrogen or $-(C_1-C_{12})$ alkyl, alkoxy, aryl, heteroaryl; or

(c) $-C(=O)OR_{14}$ where R_{14} is hydrogen, $-(C_1-C_{12})$ alkyl, substituted alkyl, or heteroalkyl, $-(C_1-C_{12})$ alkenyl, substituted alkenyl, or heteroalkenyl, $-(C_1-C_{12})$ alkynyl, substituted alkynyl, or heteroalkynyl, alkoxy, or $-(C_1-C_8$ alkyl or substituted alkyl$)_{n9}-(C_3-C_{12}$ arylene or heteroarylene$)-(C_1-C_8$ alkyl or substituted alkyl$)_{n10}$ where n9 and n10 are independently 0 or 1. Preferably, R_7 is $-C(=O)OR_{14}$ where R_{14} is hydrogen or $-(C_1-C_{12})$ alkyl, alkoxy, aryl, or heteroaryl. More preferably, $-C(=O)OR_{14}$ where R_{14} is alkyl, even more preferably R_7 is *tert*-butoxycarbonyl. The stereochemistry at the C2 carbon atom of the pyrrolidine ring, i.e., carbon carrying the R_7 group is either (*R*) or (*S*), preferably (*S*).

(C) Another preferred group of compounds is represented by Formula (IIb):



(IIb)

wherein:

R_1 is $-R_9$, -OH, $-OR_9$, $-R_8OR_9$, -SH, $-SR_9$, $-NH_2$, $-NHR_9$ $-NR_9R_{10}$, $-NHC(=O)H$, $-NR_9C(=O)H$, $-NHC(=O)R_9$, $-NR_9C(=O)R_{10}$, $-NHC(=O)NH_2$, $-NR_9C(=O)NH_2$, $-NHC(=O)NHR_9$, $-NHC(=O)NR_9R_{10}$, $-NR_9C(=O)NR_{9a}R_{10}$, $-NHC(=O)OR_9$, $-NR_9C(=O)OR_{10}$, $-NHS(=O)_2R_9$, $-NR_9S(=O)_2R_{10}$, $-NHS(=O)_2OR_9$, or $-NR_9S(=O)_2OR_{10}$ where R_8 is selected from the group consisting of $-C_1$-C_{12} alkyl, substituted alkyl, or heteroalkyl, $-C_1$-C_{12} alkenyl, substituted alkenyl, or heteroalkenyl, $-C_1$-C_{12} alkynyl, substituted alkynyl, or heteroalkynyl, and $-(C_1$-C_8 alkyl or substituted alkyl$)_{n1}$-(C_3-C_{12} arylene or heteroarylene)-(C_1-C_8 alkyl or substituted alkyl$)_{n2}$ where n1 and n2 are independently 0 or 1; and R_9, R_{9a}, and R_{10} are each independently selected from the group consisting of $-C_1$-C_{12} alkyl, substituted alkyl, or heteroalkyl, $-C_1$-C_{12} alkenyl, substituted alkenyl, or heteroalkenyl, $-C_1$-C_{12} alkynyl, substituted alkynyl, or heteroalkynyl, and $-(C_1$-C_8 alkyl or substituted alkyl$)_{n3}$-(C_3-C_{12} arylene or heteroarylene)-(C_1-C_8 alkyl or substituted alkyl$)_{n4}$ where n3 and n4 are independently 0 or 1;

R_2 is -H or $-R_9$ where R_9 is as defined above;

R_3 is $-R_{11}$, -OH, $-OR_{11}$, $-R_{12}OR_{11}$, -SH, $-SR_{11}$, $-NH_2$, $-NHR_{11}$, $-NR_aR_b$, $-NHC(=O)H$, $-NR_{11}C(=O)H$, $-NHC(=O)R_{11}$, $-NR_{11}C(=O)R_{13}$, $-NHC(=O)NH_2$, $-NR_{11}C(=O)NH_2$, $-NHC(=O)NHR_{11}$, $-NHC(=O)NR_{11}R_{13}$, $-NR_{11}C(=O)NR_{11a}R_{13}$, $-NHC(=O)OR_{11}$, $-NR_{11}C(=O)OR_{13}$, $-NHS(=O)_2R_{11}$, $-NR_{11}S(=O)_2R_{13}$, $-NHS(=O)_2OR_{11}$, or $-NR_{11}S(=O)_2OR_{13}$ where R_{12} is selected from the group consisting of $-C_1$-C_{12} alkylene, substituted alkylene, or heteroalkylene, $-C_1$-C_{12} alkenylene, substituted alkenylene, or heteroalkenylene, $-C_1$-C_{12} alkynylene, substituted alkynylene, or heteroalkynylene, and $-(C_1$-C_8 alkylene or substituted alkylene$)_{n5}$-(C_3-C_{12} arylene or heteroarylene)-(C_1-C_8 alkyl or substituted alkyl$)_{n6}$ where n5 and n6 are independently 0 or 1; and R_{11}, R_{11a}, and R_{13} are independently selected from the group consisting of $-C_1$-C_{12} alkyl, substituted alkyl, or heteroalkyl, $-C_1$-C_{12} alkenyl, substituted alkenyl, or heteroalkenyl, $-C_1$-C_{12} alkynyl, substituted alkynyl, or heteroalkynyl, and $-(C_1$-C_8 alkyl or substituted alkyl$)_{n7}$-(C_3-C_{12} arylene or heteroarylene)-(C_1-C_8 alkyl or substituted alkyl$)_{n8}$ where n7 and n8 are independently 0 or 1;

R_4 is hydrogen or $-R_{11}$ where R_{11} is as defined above;

R_7 is $-C(=O)H$, $-C(=O)R_{14}$, $-C(=O)NH_2$, $-C(=O)NHR_{14}$, $-C(=O)NR_{14}R_{15}$, $-C(=O)SH$, or $-C(=O)SR_{14}$ where where R_{14} and R_{15} are independently selected from

the group consisting of -C_1-C_{12} alkyl, substituted alkyl, or heteroalkyl, -C_1-C_{12} alkenyl, substituted alkenyl, or heteroalkenyl, -C_1-C_{12} alkynyl, substituted alkynyl, or heteroalkynyl, and -(C_1-C_8 alkyl or substituted alkyl)$_{n9}$-(C_3-C_{12} arylene or heteroarylene)-(C_1-C_8 alkyl or substituted alkyl)$_{n10}$ where n9 and n10 are independently 0 or 1; and where R_7 is -C(=O)N$R_{14}R_{15}$, then the R_{14} and R_{15} groups additionally can combine to form a substituted or unsubstituted C_4-C_{10} cyclic alkyl, cyclic heteroalkyl, aryl or heteroaryl group; or

a pharmaceutically acceptable salt thereof.

Within this group of compounds, a preferred group of compounds is that wherein the embodiments of (i) - (iv) defined below are employed either singularly or in any combination:

(i) A preferred group of compounds is that wherein R_1 is hydroxy and the stereochemistry at the carbon carrying the R_1 group is (*R*) or (*S*), preferably (*S*).

(ii) Another preferred group of compounds is that wherein R_2 is hydrogen.

(iii) Another preferred group of compounds is that wherein R_3 is hydrogen or R_9 where R_9 is –C_1-C_{12} alkyl or –(C_1-C_8 alkylene)$_{n5}$-(C_3-C_{12} aryl or heteroaryl) where n5 is 0 or 1, preferably methyl, ethyl, *n*-propyl, *iso*-propyl, *n*-butyl, *iso*-butyl, *tert*-butyl, *n*-pentyl, *iso*-pentyl, *neo*-pentyl, *n*-hexyl, 2-, 3-, 4-, or 5-methylpentyl, 4-dimethylbutyl, benzyl, 3-phenylpropyl, 2-phenylethyl, or 4-phenylbutyl, more preferably *n*-butyl. The stereochemistry at the carbon carrying the R_3 group is (*R*) or (*S*), preferably (*R*).

(iv) Yet another preferred group of compounds is that wherein R_7 is:

(a) -C(=O)NHR_{14} where R_{14} is selected from the group consisting of -(C_1-C_{12}) alkyl, substituted alkyl, or heteroalkyl, -(C_1-C_{12}) alkenyl, substituted alkenyl, or heteroalkenyl, -(C_1-C_{12}) alkynyl, substituted alkynyl, or heteroalkynyl, alkoxy, and -(C_1-C_8 alkyl or substituted alkyl)$_{n9}$-(C_3-C_{12} arylene or heteroarylene)-(C_1-C_8 alkyl or substituted alkyl)$_{n10}$ where n9 and n10 are independently 0 or 1. Preferably, R_7 is -C(=O)NHR_{14} where R_{14} is –(C_1-C_{12}) alkyl, alkoxy, aryl, or heteroaryl. More preferably, R_7 is -C(=O)NHR_{14} where R_{14} is –(C_1-C_{12}) alkyl, aryl, or heteroaryl. Even more preferably R_7 is *n*-butylaminocarbonyl, *tert*-butylaminocarbonyl, benzylaminocarbonyl, 1,1-dimethylpropylaminocarbonyl, 2-(cyclohexen-1-yl)-ethylaminocarbonyl, indan-5-ylaminocarbonyl, 4,5-dimethylthiazol-2-ylaminocarbonyl, 4-phenoxyphenylaminocarbonyl, cyclopropylmethyl-aminocarbonyl, pyridin-2-ylaminocarbonyl, pyridin-3-ylaminocarbonyl, pyridin-4-

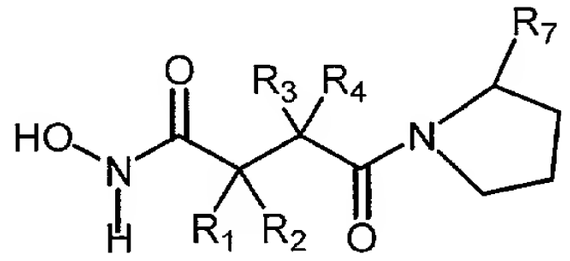
ylmethylaminocarbonyl, morpholin-4-ylcarbonyl, 3,4-methylenedioxy-phenylaminocarbonyl, quinolin-3-ylaminocarbonyl, methylaminocarbonyl, 4-biphenylaminocarbonyl, 3-phenoxyphenylaminocarbonyl, 3,4-dichlorophenyl-aminocarbonyl, 4-*tert*-butylphenylaminocarbonyl, 4-*tert*-butylaminocarbonyl, indan-2-ylaminocarbonyl, 2,2-dimethylpropylaminocarbonyl, 4-phenylthiazol-2-ylamino-carbonyl, 5-phenylthiadiazol-2-ylaminocarbonyl, 5-ethylthiadiazol-3-ylamino-carbonyl, thiadiazol-2-ylaminocarbonyl, 3-trifluoromethoxyphenyl-aminocarbonyl, 2,5-dimethylphenylaminocarbonyl, 2,5-dimethoxyphenylamino-carbonyl, 3,4-dichlorophenylaminocarbonyl, benzthiazol-2-ylaminocarbonyl, 3-phenoxy-phenylaminocarbonyl, 2-hydroxybutylaminocarbonyl, 4-hydroxybutyl-aminocarbonyl, 1,4-benzodioxan-6-ylaminocarbonyl, isoquinolin-6-ylaminocarbonyl, methylaminocarbonyl, thiazol-2-ylaminocarbonyl, 4-methylthiazol-2-yl-aminocarbonyl, 3-methylbutyl-aminocarbonyl, *n*-pentylaminocarbonyl, cyclohexylaminocarbonyl, 5-methylthiazol-2-ylaminocarbonyl, 4-methylthiazol-2-yl-aminocarbonyl, 2,4-dimethoxyphenyl-aminocarbonyl, 3,4-methylenedioxyphen-5-yl-methylaminocarbonyl, allylaminocarbonyl, 2-methylallylaminocarbonyl, pyrrolidin-1-ylcarbonyl, ethylaminocarbonyl, phenylaminocarbonyl, indan-1-ylaminocarbonyl, 2-methoxyethylaminocarbonyl, indan-5-ylaminocarbonyl, 3,4-difluorophenyl-aminocarbonyl, 5-methylisoxazol-5-ylaminocarbonyl, 3-fluorophenylaminocarbonyl, 4-fluorophenylaminocarbonyl, *N*-methyl-*N*-phenylaminocarbonyl, 2-propylamino-carbonyl, 2-phenylpropylaminocarbonyl, *n*-propylaminocarbonyl, *N*-ethyl-*N*-(*n*-butyl)aminocarbonyl, benzylaminocarbonyl, thiazolidin-1-ylcarbonyl, piperazin-1-yl-carbonyl, piperidin-1-ylcarbonyl, azetidin-1-ylcarbonyl, homopiperdin-1-ylcarbonyl, pyrimidin-2-ylaminocarbonyl, 4-methylpiperazin-1-ylcarbonyl, 4-methylpyrimidin-2-ylaminocarbonyl, pyrimidin-4-ylaminocarbonyl, pyrazin-2-ylaminocarbonyl, imidazol-2-ylaminocarbonyl. In particular, R_7 is piperidin-1-ylcarbonyl, azetidin-1-ylcarbonyl, ethylaminocarbonyl, phenylaminocarbonyl, pyrimidin-2-yl-aminocarbonyl, or thiazol-2-ylaminocarbonyl.

More particularly, R_7 is phenylaminocarbonyl or pyrimidin-2-ylamino-carbonyl. The stereochemistry at the C2 carbon atom of the pyrrolidine ring, i.e., carbon carrying the R_7 group is either (*R*) or (*S*), preferably (*S*); or

(b) R_7 is $-C(=O)OR_{14}$ where R_{14} is selected from the group consisting of hydrogen, $-(C_1-C_{12})$ alkyl, substituted alkyl, or heteroalkyl, $-(C_1-C_{12})$ alkenyl, substituted alkenyl, or heteroalkenyl, $-(C_1-C_{12})$ alkynyl, substituted alkynyl, or

heteroalkynyl, alkoxy, and -(C_1-C_8 alkyl or substituted alkyl)$_{n9}$-(C_3-C_{12} arylene or heteroarylene)-(C_1-C_8 alkyl or substituted alkyl)$_{n10}$ where n9 and n10 are independently 0 or 1. Preferably, R_7 is -C(=O)OR_{14} where R_{17} is hydrogen, –(C_1-C_{12}) alkyl, alkoxy, aryl, or heteroaryl. More preferably, -C(=O)OR_{14} where R_{14} is alkyl, even more preferably R_7 is *tert*-butoxycarbonyl. The stereochemistry at the C2 carbon atom of the pyrrolidine ring, i.e., carbon carrying the R_7 group is either (*R*) or (*S*), preferably (*S*).

(D) Another preferred group of compounds if represented by Formula (IIc):



(IIc)

wherein:

R_1 is -OH, -OR_9, -SH or –SR_9 wherein R_9 is selected from the group consisting of -C_1-C_{12} alkyl, substituted alkyl, or heteroalkyl, -C_1-C_{12} alkenyl, substituted alkenyl, or heteroalkenyl, -C_1-C_{12} alkynyl, substituted alkynyl, or heteroalkynyl, and -(C_1-C_8 alkyl or substituted alkyl)$_{n1}$-(C_3-C_{12} arylene or heteroarylene)-(C_1-C_8 alkyl or substituted alkyl)$_{n2}$ where n1 and n2 are independently 0 or 1;

R_2 is hydrogen;

R_3 is –R_{11}, -OH, -OR_{11}, -$R_{12}OR_{11}$, -SH, -SR_{11}, -NH_2, -NHR_{11}, –$NR_{11}R_{13}$, -NHC(=O)H, -NR_{11}C(=O)H, -NHC(=O)R_{11}, -NR_{11}C(=O)R_{13}, -NHC(=O)NH_2, -NR_{11}C(=O)NH_2, -NHC(=O)NHR_{11}, -NHC(=O)$NR_{11}R_{13}$, -NR_{11}C(=O)$NR_{11a}R_{13}$, -NHC(=O)OR_{11}, -NR_{11}C(=O)OR_{13}, -NHS(=O)$_2R_{11}$, -NR_{11}S(=O)$_2R_{13}$, -NHS(=O)$_2OR_{11}$, or –NR_{11}S(=O)$_2OR_{13}$ where R_{12} is selected from the group consisting of -C1-C_{12} alkylene, substituted alkylene, or heteroalkylene, -C_1-C_{12} alkenylene, substituted alkenylene, or heteroalkenylene, -C_1-C_{12} alkynylene, substituted alkynylene, or heteroalkynylene, and -(C_1-C_8 alkylene or substituted alkylene)$_{n5}$-(C_3-C_{12} arylene or heteroarylene)-(C_1-C_8 alkyl or substituted alkyl)$_{n6}$ where n5 and n6 are independently 0 or 1; and R_{11} and R_{13} are independently selected from the group consisting of -C1-C_{12} alkyl, substituted alkyl, or heteroalkyl, -C_1-C_{12}

alkenyl, substituted alkenyl, or heteroalkenyl, -C_1-C_{12} alkynyl, substituted alkynyl, or heteroalkynyl, and -(C_1-C_8 alkyl or substituted alkyl)$_{n7}$-(C_3-C_{12} arylene or heteroarylene)-(C_1-C_8 alkyl or substituted alkyl)$_{n8}$ where n7 and n8 are independently 0 or 1;

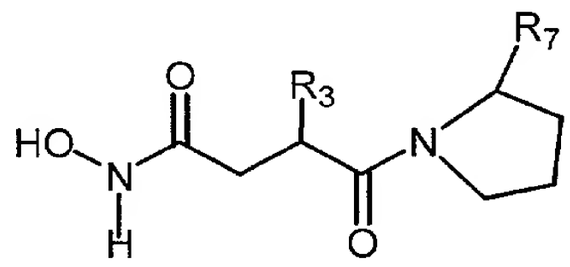
R_4 is hydrogen or –R_{11} wherein R_{11} is as defined above; and

R_7 is –C(=O)OR_{14}, where R_{14} is selected from the group consisting of -C_1-C_{12} alkyl, substituted alkyl, or heteroalkyl, -C_1-C_{12} alkenyl, substituted alkenyl, or heteroalkenyl, -C_1-C_{12} alkynyl, substituted alkynyl, or heteroalkynyl, and -(C_1-C_8 alkyl or substituted alkyl)$_{n9}$-(C_3-C_{12} arylene or heteroarylene)-(C_1-C_8 alkyl or substituted alkyl)$_{n10}$ where n9 and n10 are independently 0 or 1; or

a pharmaceutically acceptable salt thereof.

In another embodiment of this series of compounds, R_1 is -OH or –OR_9. In another embodiment of this series of compounds, R_3 is -C_1-C_{12} alkyl, such as C_4 alkyl and R_4 is H. In another embodiment of this series of compounds, R_{14} is –C(=O)O-C_1-C_{12} alkyl, such as –C(=O)O-C_1-C_4 alkyl, for example –C(=O)O-t-butyl.

(E) Another preferred group of compounds if represented by Formula (IId):



(IId)

wherein:

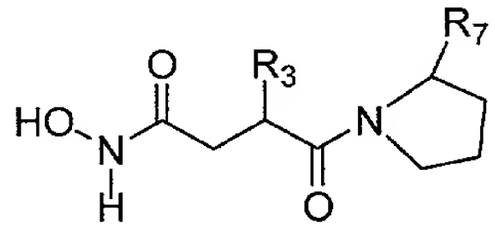
R_3 is –R_{11} where R_{11} is selected from the group consisting of -C_1-C_{12} alkyl, substituted alkyl, or heteroalkyl, -C_1-C_{12} alkenyl, substituted alkenyl, or heteroalkenyl, -C_1-C_{12} alkynyl, substituted alkynyl, or heteroalkynyl, and -(C_1-C_8 alkyl or substituted alkyl)$_{n7}$-(C_3-C_{12} arylene or heteroarylene)-(C_1-C_8 alkyl or substituted alkyl)$_{n8}$ where n7 and n8 are independently 0 or 1; and

R_7 is –C(=O)OR_{14} where R_{14} is selected from the group consisting of -C_1-C_{12} alkyl, substituted alkyl, or heteroalkyl, -C_1-C_{12} alkenyl, substituted alkenyl, or heteroalkenyl, -C_1-C_{12} alkynyl, substituted alkynyl, or heteroalkynyl, and -(C_1-C_8 alkyl or substituted alkyl)$_{n9}$-(C_3-C_{12} arylene or heteroarylene)-(C_1-C_8 alkyl or

substituted alkyl)$_{n10}$ where n9 and n10 are independently 0 or 1; or a pharmaceutically acceptable salt thereof.

In one embodiment , R_3 is –(C_1-C_{12})alkyl, preferably *n*-butyl. In another embodiment of this series of compounds, R_7 is –C(O)O-C_1-C_{12} alkyl, such as –C(O)O-C_1-C_4 alkyl, for example –C(O)O-*tert*-butyl.

(F) Another preferred group of compounds if represented by Formula (IIe):



(IIe)

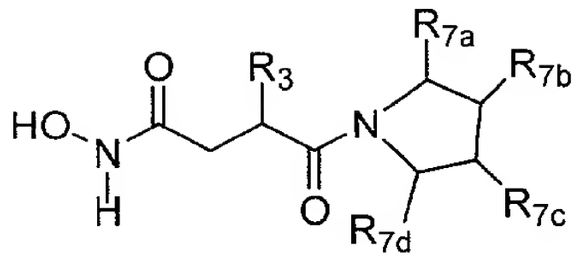
wherein:

R_3 is –R_{11} where –R_{11} is selected from the group consisting of -C_1-C_{12} alkyl, substituted alkyl, or heteroalkyl, -C_1-C_{12} alkenyl, substituted alkenyl, or heteroalkenyl, -C_1-C_{12} alkynyl, substituted alkynyl, or heteroalkynyl, and -(C_1-C_8 alkyl or substituted alkyl)$_{n7}$-(C_3-C_{12} arylene or heteroarylene)-(C_1-C_8 alkyl or substituted alkyl)$_{n8}$ where n7 and n8 are independently 0 or 1;

R_7 is -NH_2, -NHR_{13}, or –$NHR_{14}R_{15}$ where R_{13}, R_{14} and R_{15} are independently selected from the group consisting of -C_1-C_{12} alkyl, substituted alkyl, or heteroalkyl, -C_1-C_{12} alkenyl, substituted alkenyl, or heteroalkenyl, -C_1-C_{12} alkynyl, substituted alkynyl, or heteroalkynyl, and -(C_1-C_8 alkyl or substituted alkyl)$_{n9}$-(C_3-C_{12} arylene or heteroarylene)-(C_1-C_8 alkyl or substituted alkyl)$_{n10}$ where n9 and n10 are independently 0 or 1; or where R_{14} and R_{15} combine to form a substituted or unsubstituted C_4-C_{10} cyclic alkyl, cyclic heteroalkyl, aryl or heteroaryl group; or a pharmaceutically acceptable salt thereof.

In one embodiment of this series of compounds, R_3 is C_1-C_{12} alkyl, preferably *n*-butyl. In another embodiment of this series of compounds, R_7 is –NHR_{13} where R_{13} is as defined above.

(G) Another preferred group of compounds if represented by Formula (IIf):



(IIf)

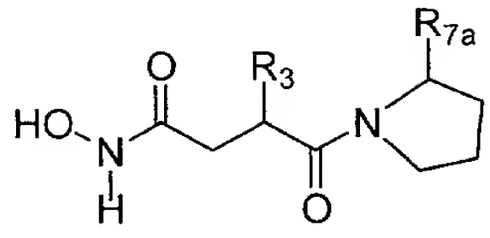
wherein:

R_3 is $-R_{11}$ wherein R_{11} is selected from the group consisting of hydrogen, -C_1-C_{12} alkyl, substituted alkyl, or heteroalkyl, -C_1-C_{12} alkenyl, substituted alkenyl, or heteroalkenyl, -C_1-C_{12} alkynyl, substituted alkynyl, or heteroalkynyl, and -(C_1-C_8 alkyl or substituted alkyl)$_{n7}$-(C_3-C_{12} arylene or heteroarylene)-(C_1-C_8 alkyl or substituted alkyl)$_{n8}$ where n7 and n8 are independently 0 or 1;

R_{7a}, R_{7b}, R_{7c} and R_{7d} are independently selected from the group consisting of hydrogen, -C_1-C_{12} alkyl, substituted alkyl, or heteroalkyl, -C_1-C_{12} alkenyl, substituted alkenyl, or heteroalkenyl, -C_1-C_{12} alkynyl, substituted alkynyl, or heteroalkynyl, and -(C_1-C_8 alkyl or substituted alkyl)$_{n9}$-(C_3-C_{12} arylene or heteroarylene)-(C_1-C_8 alkyl or substituted alkyl)$_{n10}$ where n9 and n10 are independently 0 or 1; or two vicinal R_7 groups can combine to form a substituted or unsubstituted C_4-C_{10} cyclic alkyl, cyclic heteroalkyl, aryl or heteroaryl group; or a pharmaceutically acceptable salt thereof.

In one embodiment of this series of compounds, R_3 is *n*-butyl. In another embodiment of this series of compounds, at least one R_7 is selected from the group consisting of -C(=O)OR_{14}, -OH, -OR_{14}, -R_{14}, -NH(C=O)OR_{14}, or -NH(C=O)R_{15}, where R_{14} and R_{15} are independently selected from the group consisting of -C_1-C_{12} alkyl, substituted alkyl, or heteroalkyl, -C_1-C_{12} alkenyl, substituted alkenyl, or heteroalkenyl, C_1-C_{12} alkynyl, substituted alkynyl, or heteroalkynyl, and (C_1-C_8 alkyl or substituted alkyl)$_{n9}$-(C_3-C_{12} arylene or heteroarylene)-(C_1-C_8 alkyl or substituted alkyl)$_{n10}$ where n9 and n10 are independently 0 or 1.

(H) Another preferred group of compounds if represented by Formula (IIg):



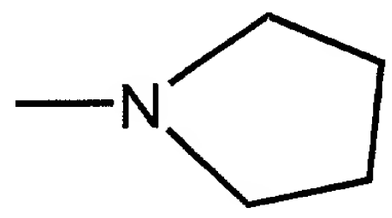
(IIg)

wherein:

R_3 is $-R_{11}$ where R_{11} is selected from the group consisting of hydrogen, $-C_1$-C_{12} alkyl, substituted alkyl, or heteroalkyl, $-C_1$-C_{12} alkenyl, substituted alkenyl, or heteroalkenyl, $-C_1$-C_{12} alkynyl, substituted alkynyl, or heteroalkynyl, and $-(C_1$-C_8 alkyl or substituted alkyl$)_{n7}$-(C_3-C_{12} arylene or heteroarylene)-(C_1-C_8 alkyl or substituted alkyl$)_{n8}$ where n7 and n8 are independently 0 or 1; and

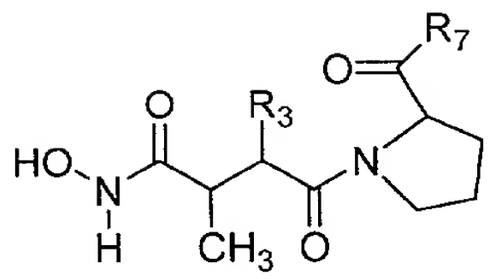
R_{7a} is selected from the group consisting of hydrogen, $-C_1$-C_{12} alkyl, substituted alkyl, or heteroalkyl, $-C_1$-C_{12} alkenyl, substituted alkenyl, or heteroalkenyl, $-C_1$-C_{12} alkynyl, substituted alkynyl, or heteroalkynyl, and $-(C_1$-C_8 alkyl or substituted alkyl$)_{n9}$-(C_3-C_{12} arylene or heteroarylene)-(C_1-C_8 alkyl or substituted alkyl$)_{n10}$ where n9 and n10 are independently 0 or 1; or a pharmaceutically acceptable salt thereof.

In another embodiment of this series of compounds, R_{7a} is $-CH_2$-R_d where R_d is selected from the group consisting of H, $-C_1$-C_{12} alkyl, substituted alkyl, or heteroalkyl, $-C_1$-C_{12} alkenyl, substituted alkenyl, or heteroalkenyl, $-C_1$-C_{12} alkynyl, substituted alkynyl, or heteroalkynyl, and $-(C_1$-C_8 alkyl or substituted alkyl$)_{n9}$-(C_3-C_{12} arylene or heteroarylene)-(C_1-C_8 alkyl or substituted alkyl$)_{n10}$ where n9 and n10 are independently 0 or 1. In another embodiment of this series of compounds, R_d is selected from the group consisting of $-O-CH_3$, -OH, $-NH-(C=O)-CH_3$, and



.

(I) Another preferred group of compounds if represented by Formula (IIh):



(IIh)

wherein:

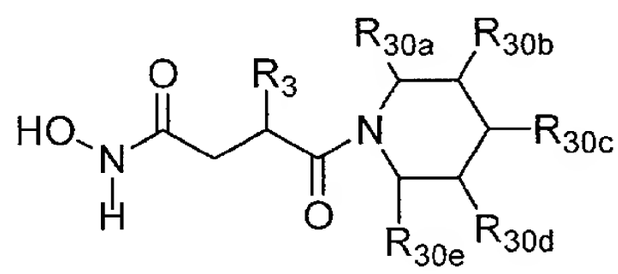
R_3 is $-R_{11}$ where R_{11} is selected from the group consisting of hydrogen, -C_1-C_{12} alkyl, substituted alkyl, or heteroalkyl, -C_1-C_{12} alkenyl, substituted alkenyl, or heteroalkenyl, -C_1-C_{12} alkynyl, substituted alkynyl, or heteroalkynyl, and -(C_1-C_8 alkyl or substituted alkyl)$_{n7}$-(C_3-C_{12} arylene or heteroarylene)-(C_1-C_8 alkyl or substituted alkyl)$_{n8}$ where n7 and n8 are independently 0 or 1; and

R_7 is selected from the group consisting of $-R_{14}$ or $-OR_{14}$ where R_{14} is selected from the group consisting of -C_1-C_{12} alkyl, substituted alkyl, or heteroalkyl, -C_1-C_{12} alkenyl, substituted alkenyl, or heteroalkenyl, -C_1-C_{12} alkynyl, substituted alkynyl, or heteroalkynyl, and -(C_1-C_8 alkyl or substituted alkyl)$_{n9}$-(C_3-C_{12} arylene or heteroarylene)-(C_1-C_8 alkyl or substituted alkyl)$_{n10}$ where n9 and n10 are independently 0 or 1; or

a pharmaceutically acceptable salt thereof.

In one embodiment of this series of compounds, R_3 is *n*-butyl. In another embodiment of this series of compounds, R_7 is -OCH_3 or -O-*tert*-butyl.

(J) Another preferred group of compounds if represented by Formula (IIi):



(IIi)

wherein:

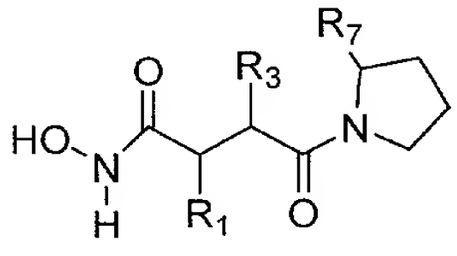
R_3 is $-R_{11}$ where R_{11} is hydrogen, -C_1-C_{12} alkyl, substituted alkyl, or heteroalkyl, -C_1-C_{12} alkenyl, substituted alkenyl, or heteroalkenyl, -C_1-C_{12} alkynyl, substituted alkynyl, or heteroalkynyl, or -(C_1-C_8 alkyl or substituted alkyl)$_{n7}$-(C_3-C_{12}

arylene or heteroarylene)-(C_1-C_8 alkyl or substituted alkyl)$_{n8}$ where n7 and n8 are independently 0 or 1; and

R_{30a}, R_{30b}, R_{30c}, R_{30d}, and R_{30e} are independently selected from the group consisting of hydrogen, -C_1-C_{12} alkyl, substituted alkyl, or heteroalkyl, -C_1-C_{12} alkenyl, substituted alkenyl, or heteroalkenyl, -C_1-C_{12} alkynyl, substituted alkynyl, or heteroalkynyl, and -(C_1-C_8 alkyl or substituted alkyl)$_{n9}$-(C_3-C_{12} arylene or heteroarylene)-(C_1-C_8 alkyl or substituted alkyl)$_{n10}$ where n9 and n10 are independently 0 or 1; or where two vicinal R_{30} groups can combine to form a substituted or unsubstituted C_4-C_{10} cyclic alkyl, cyclic heteroalkyl, aryl or heteroaryl group; and all salts and stereoisomers thereof.

In one embodiment of this series of compounds, at least one R_{30} is selected from the group consisting of -C(=O)OR_{15} and -C(=O)R_{15}, where R_{15} is independently selected from the group consisting of C_1-C_{12} alkyl, substituted alkyl, or heteroalkyl, C_1-C_{12} alkenyl, substituted alkenyl, or heteroalkenyl, C_1-C_{12} alkynyl, substituted alkynyl, or heteroalkynyl, and (C_1-C_8 alkyl or substituted alkyl)$_{n9}$-(C_3-C_{12} arylene or heteroarylene)-(C_1-C_8 alkyl or substituted alkyl)$_{n10}$ where n9 and n10 are independently 0 or 1.

(K) Another preferred group of compounds if represented by Formula (IIj):



(IIj)

where:

R_1 is halo;

R_3 is hydrogen, R_{11}, -OH, -OR_{11}, -R_{12}OR_{11}, -SH, -SR_{11}, -NH_2, -NHR_{11}, –N$R_{11}R_{13}$, -NHC(=O)H, -NR_{11}C(=O)H, -NHC(=O)R_{11}, -NR_{11}C(=O)R_{13}, -NHC(=O)NH_2, -NR_{11}C(=O)NH_2, -NHC(=O)NHR_{11}, -NHC(=O)N$R_{11}R_{13}$, -NR_{11}C(=O)N$R_{11a}R_{13}$, -NHC(=O)OR_{11}, -NR_{11}C(=O)OR_{13}, -NHS(=O)$_2R_{13}$, -NR_{11}S(=O)$_2R_{13}$, -NHS(=O)$_2$OR_{11}, or –NR_{11}S(=O)$_2$OR_{13}, where R_{12} is selected from the group consisting of -C_1-C_{12} alkylene, substituted alkylene, or heteroalkylene, -C_1-C_{12} alkenylene, substituted alkenylene, or heteroalkenylene, -C_1-C_{12} alkynylene,

substituted alkynylene, or heteroalkynylene, and -(C_1-C_8 alkylene or substituted alkylene)$_{n5}$-(C_3-C_{12} arylene or heteroarylene)-(C_1-C_8 alkyl or substituted alkyl)$_{n6}$ where n5 and n6 are independently 0 or 1; and R_{11}, R_{11a} and R_{13} are independently selected from the group consisting of -C_1-C_{12} alkyl, substituted alkyl, or heteroalkyl, -C_1-C_{12} alkenyl, substituted alkenyl, or heteroalkenyl, -C_1-C_{12} alkynyl, substituted alkynyl, or heteroalkynyl, and -(C_1-C_8 alkyl or substituted alkyl)$_{n7}$-(C_3-C_{12} arylene or heteroarylene)-(C_1-C_8 alkyl or substituted alkyl)$_{n8}$ where n7 and n8 are independently 0 or 1;

R_7 is hydrogen, R_{14}, -OH, -OR_{14}, -SH, -SR_{14}, -NH_2, -NHR_{14}, -$NR_{14}R_{15}$, -C(=O)H, -C(=O)R_{14}, -C(=O)NH_2, -C(=O)NHR_{14}, -C(=O)$NR_{14}R_{15}$, -C(=O)OH, -C(=O)OR_{14}, -C(=O)SH, -C(=O)SR_{14}, -C(=O)CH_3, -C(=O)CH_2R_{14}, -C(=O)$CHR_{14}R_{15}$, -C(=O)$CR_{14}R_{15}R_{16}$, -C(=O)OCH_3, -C(=O)OCH_2R_{14}, -C(=O)$OCHR_{14}R_{15}$, -C(=O)$OCR_{14}R_{15}R_{16}$, -$S(=O)_2NH_2$, -$S(=O)_2NHR_{14}$, -$S(=O)_2NR_{14}R_{15}$, -NHC(=O)H, -$N(R_{14})$C(=O)H, -NHC(=O)R_{15}, -$N(R_{14})$C(=O)R_{15}, -NHC(=O)OR_{14}, -$NHS(=O)_2H$, -$N(R_{14})S(=O)_2H$, -$NHS(=O)_2OR_{15}$, -$N(R_{14})S(=O)_2OR_{15}$, -$N(H)S(=O)_2R_{15}$, or -$N(R_{14})S(=O)_2R_{15}$, or where two vicinal R_6 or R_7 groups combine to form a substituted or unsubstituted -C_4-C_{10} cyclic alkyl, cyclic heteroalkyl, aryl or heteroaryl group where R_{14}, R_{15} and R_{16} are each independently selected from the group consisting of -C_1-C_{12} alkyl, substituted alkyl, or heteroalkyl, -C_1-C_{12} alkenyl, substituted alkenyl, or heteroalkenyl, -C_1-C_{12} alkynyl, substituted alkynyl, or heteroalkynyl, and -(C_1-C_8 alkyl or substituted alkyl)$_{n9}$-(C_3-C_{12} arylene or heteroarylene)-(C_1-C_8 alkyl or substituted alkyl)$_{n10}$ where n9 and n10 are independently 0 or 1; or when R_{14} and R_{15} are attached to a nitrogen atom they can combine to form a substituted or unsubstituted C_4-C_{10} cyclic alkyl, cyclic heteroalkyl, aryl or heteroaryl group; or

a pharmaceutically acceptable salt thereof.

Within this group of compounds, a preferred group of compounds is that wherein the embodiments of (i) - (iii) defined below are employed either singularly or in any combination:

(i) A preferred group of compounds is that wherein R_1 is fluoro. The stereochemistry at the carbon carrying the R_1 group is (*R*) or (*S*), preferably (*S*).

(ii) Another preferred group of compounds is that wherein R_3 is hydrogen or R_9 where R_9 is –C_1-C_{12} alkyl or –(C_1-C_8 alkylene)$_{n5}$-(C_3-C_{12} aryl or heteroaryl) where n5 is 0 or 1, preferably methyl, ethyl, *n*-propyl, *iso*-propyl, *n*-butyl, *iso*-butyl,

tert-butyl, *n*-pentyl, *iso*-pentyl, *neo*-pentyl, *n*-hexyl, 2-, 3-, 4-, or 5-methylpentyl, 4,4-dimethylbutyl, benzyl, 3-phenylpropyl, 2-phenylethyl, or 4-phenylbutyl, more preferably *n*-butyl. The stereochemistry at the carbon carrying the R_3 group is (*R*) or (*S*), preferably (*R*); and

(iii) R_7 is:

(a) $-C(=O)NR_{14}R_{15}$, where R_{14} and R_{15} are independently hydrogen, $-(C_1-C_{12})$ alkyl, substituted alkyl, or heteroalkyl, $-(C_1-C_{12})$ alkenyl, substituted alkenyl, or heteroalkenyl, $-(C_1-C_{12})$ alkynyl, substituted alkynyl, or heteroalkynyl, alkoxy, or $-(C_1-C_8$ alkyl or substituted alkyl$)_{n9}-(C_3-C_{12}$ arylene or heteroarylene$)-(C_1-C_8$ alkyl or substituted alkyl$)_{n10}$ where n9 and n10 are independently 0 or 1; or R_{14} and R_{15} combine to form a substituted or unsubstituted $-(C_4-C_{10})$cyclic alkyl, cyclic heteroalkyl, aryl or heteroaryl group.

Preferably, R_7 is $-C(=O)NR_{14}R_{15}$ where R_{14} and R_{15} are each independently hydrogen or $-(C_1-C_{12})$ alkyl, alkoxy, aryl, heteroaryl or R_{14} and R_{15}, when attached to the same carbon, combine to form a cyclic heteroalkyl, aryl or heteroaryl group. More preferably, R_7 is $-C(=O)NHR_{15}$ where R_{15} is H or $-(C_1-C_{12})$ alkyl, aryl, or heteroaryl or $-C(=O)NR_{14}R_{15}$ where R_{14} and R_{15}form a substituted or unsubstituted $-(C_4-C_{10})$cyclic heteroalkyl.

Even more preferably R_7 is *n*-butylaminocarbonyl, *tert*-butylaminocarbonyl, benzylaminocarbonyl, 1,1-dimethylpropylaminocarbonyl, 2-(cyclohexen-1-yl)-ethylaminocarbonyl, indan-5-ylaminocarbonyl, 4,5-dimethylthiazol-2-ylaminocarbonyl, 4-phenoxyphenylaminocarbonyl, cyclopropylmethyl-aminocarbonyl, pyridin-2-ylaminocarbonyl, pyridin-3-ylaminocarbonyl, pyridin-4-ylmethylaminocarbonyl, morpholin-4-ylcarbonyl, 3,4-methylenedioxy-phenylaminocarbonyl, quinolin-3-ylaminocarbonyl, methylaminocarbonyl, 4-biphenylaminocarbonyl, 3-phenoxyphenylaminocarbonyl, 3,4-dichlorophenyl-aminocarbonyl, 4-*tert*-butylphenylaminocarbonyl, 4-*tert*-butylaminocarbonyl, indan-2-ylaminocarbonyl, 2,2-dimethylpropylaminocarbonyl, 4-phenylthiazol-2-ylaminocarbonyl, 5-phenylthiadiazol-2-ylaminocarbonyl, 5-ethylthiadiazol-3-ylaminocarbonyl, thiadiazol-2-ylaminocarbonyl, 3-trifluoromethoxyphenyl-aminocarbonyl, 2,5-dimethylphenylaminocarbonyl, 2,5-dimethoxyphenylamino-carbonyl, 3,4-dichlorophenylaminocarbonyl, benzthiazol-2-ylaminocarbonyl, 3-phenoxyphenylaminocarbonyl, 2-hydroxybutylaminocarbonyl, 4-hydroxybutyl-aminocarbonyl, 1,4-benzodioxan-6-ylaminocarbonyl, isoquinolin-6-yl-

aminocarbonyl, methylaminocarbonyl, thiazol-2-ylaminocarbonyl, 4-methylthiazol-2-yl-aminocarbonyl, 3-methylbutyl-aminocarbonyl, *n*-pentylaminocarbonyl, cyclohexylaminocarbonyl, 5-methylthiazol-2-ylaminocarbonyl, 4-methylthiazol-2-yl-aminocarbonyl, 2,4-dimethoxyphenyl-aminocarbonyl, 3,4-methylenedioxyphen-5-yl-methylaminocarbonyl, allylaminocarbonyl, 2-methylallylaminocarbonyl, pyrrolidin-1-ylcarbonyl, ethylaminocarbonyl, phenylaminocarbonyl, indan-1-ylaminocarbonyl, 2-methoxyethylaminocarbonyl, indan-5-ylaminocarbonyl, 3,4-difluorophenyl-aminocarbonyl, 5-methylisoxazol-5-ylaminocarbonyl, 3-fluoro-phenylaminocarbonyl, 4-fluorophenylaminocarbonyl, *N*-methyl-*N*-phenylamino-carbonyl, 2-propylamino-carbonyl, 2-phenylpropylaminocarbonyl, *n*-propylamino-carbonyl, *N*-ethyl-*N*-(*n*-butyl)aminocarbonyl, benzylaminocarbonyl, thiazolidin-1-ylcarbonyl, piperazin-1-yl-carbonyl, piperidin-1-ylcarbonyl, azetidin-1-ylcarbonyl, homopiperdin-1-ylcarbonyl, pyrimidin-2-ylaminocarbonyl, 4-methylpiperazin-1-ylcarbonyl, 4-methylpyrimidin-2-ylaminocarbonyl, pyrimidin-4-ylaminocarbonyl, pyrazin-2-ylaminocarbonyl, imidazol-2-ylaminocarbonyl.

In particular, R_7 is piperidin-1-ylcarbonyl, azetidin-1-ylcarbonyl, ethylaminocarbonyl, phenylaminocarbonyl, pyrimidin-2-ylaminocarbonyl, or thiazol-2-ylaminocarbonyl.

More particularly, R_7 is piperidin-1-ylcarbonyl, azetidin-1-ylcarbonyl, ethylaminocarbonyl or thiazol-2-ylaminocarbonyl. The stereochemistry at the C2 carbon atom of the pyrrolidine ring, i.e., carbon carrying the R_7 group is either (*R*) or (*S*), preferably (*S*); or

(b) R_7 is $-NHC(=O)OR_{14}$ where R_{14} is hydrogen, $-(C_1-C_{12})$ alkyl, substituted alkyl, or heteroalkyl, $-(C_1-C_{12})$ alkenyl, substituted alkenyl, or heteroalkenyl, $-(C_1-C_{12})$ alkynyl, substituted alkynyl, or heteroalkynyl, alkoxy, or $-(C_1-C_8$ alkyl or substituted alkyl$)_{n9}-(C_3-C_{12}$ arylene or heteroarylene$)-(C_1-C_8$ alkyl or substituted alkyl$)_{n10}$ where n9 and n10 are independently 0 or 1. Preferably, R_7 is $-NHC(=O)OR_{14}$ where R_{14} is hydrogen or $-(C_1-C_{12})$ alkyl, alkoxy, aryl, heteroaryl; or

(c) R_7 is $-C(=O)OR_{14}$ where R_{14} is hydrogen, $-(C_1-C_{12})$ alkyl, substituted alkyl, or heteroalkyl, $-(C_1-C_{12})$ alkenyl, substituted alkenyl, or heteroalkenyl, $-(C_1-C_{12})$ alkynyl, substituted alkynyl, or heteroalkynyl, alkoxy, or $-(C_1-C_8$ alkyl or substituted alkyl$)_{n9}-(C_3-C_{12}$ arylene or heteroarylene$)-(C_1-C_8$ alkyl or substituted alkyl$)_{n10}$ where n9 and n10 are independently 0 or 1. Preferably, R_7 is $-C(=O)OR_{17}$ where R_{14} is hydrogen or $-(C_1-C_{12})$ alkyl, alkoxy, aryl, or heteroaryl. More preferably,

-C(=O)OR_{14} where R_{14} is alkyl, even more preferably R_7 is *tert*-butoxycarbonyl. The stereochemistry at the C2 carbon atom of the pyrrolidine ring, i.e., carbon carrying the R_7 group is either (*R*) or (*S*), preferably (*S*).

Preferred compounds of the Invention are:

N-hydroxy-3-[(*S*)-(*n*-butyl)-3-(2-(*S*)-1,1-dimethylethyloxycarbonyl)-pyrrolidin-1-carbonyl)]-2-(*S*)fluoropropionamide;

N-hydroxy-3-[(*S*)-(*n*-butyl)-3-(2-(*S*)-pyridin-1-ylcarbonyl)pyrrolidin-1-carbonyl)]-2-(*S*)-fluoropropionamide;

N-hydroxy-3-[(*S*)-(*n*-butyl)-3-(2-(*S*)-azetidin-1-ylcarbonyl)-pyrrolidin-1-carbonyl)]-2-(*S*)-fluoropropionamide;

N-hydroxy-3-[(*S*)-(*n*-butyl)-3-(2-(*S*)-ethylaminocarbonyl)pyrrolidin-1-carbonyl)]-2-(*S*)-fluoropropionamide;

N-hydroxy-3-[(*S*)-(*n*-butyl)-3-(2-(*S*)-phenylaminocarbonyl)-pyrrolidin-1-carbonyl)]-2-(*S*)-hydroxypropionamide;

N-hydroxy-3-[(*S*)-(*n*-butyl)-3-(2-(*S*)-pyrimidin-2-ylaminocarbonyl)pyrrolidin-1-carbonyl)]-2-(*S*)-hydroxypropionamide; and

N-hydroxy-3-[(*S*)-(*n*-butyl)-3-(2-(*S*)-thiazol-2-ylaminocarbonyl)-pyrrolidin-1-carbonyl)]-2-(*S*)-fluoropropionamide.

GENERAL SYNTHETIC SCHEME

Compounds of this invention can be made by the methods depicted in the reaction schemes shown below.

The starting materials and reagents used in preparing these compounds are either available from commercial suppliers such as Aldrich Chemical Co., (Milwaukee, Wisconsin, USA), Bachem (Torrance, California, USA), Emka-Chemie, or Sigma (St. Louis, Missouri, USA) or are prepared by methods known to those skilled in the art following procedures set forth in references such as Fieser and Fieser's Reagents for Organic Synthesis, Volumes 1-15 (John Wiley and Sons, 1991); Rodd's Chemistry of Carbon Compounds, Volumes 1-5 and Supplementals (Elsevier Science Publishers, 1989), Organic Reactions, Volumes 1-40 (John Wiley and Sons, 1991), March's Advanced Organic Chemistry, (John Wiley and Sons, 4th Edition), and Larock's Comprehensive Organic Transformations (VCH Publishers Inc., 1989). These schemes are merely illustrative of some methods by which the compounds of

this invention can be synthesized, and various modifications to these schemes can be made and will be suggested to one skilled in the art having referred to this disclosure.

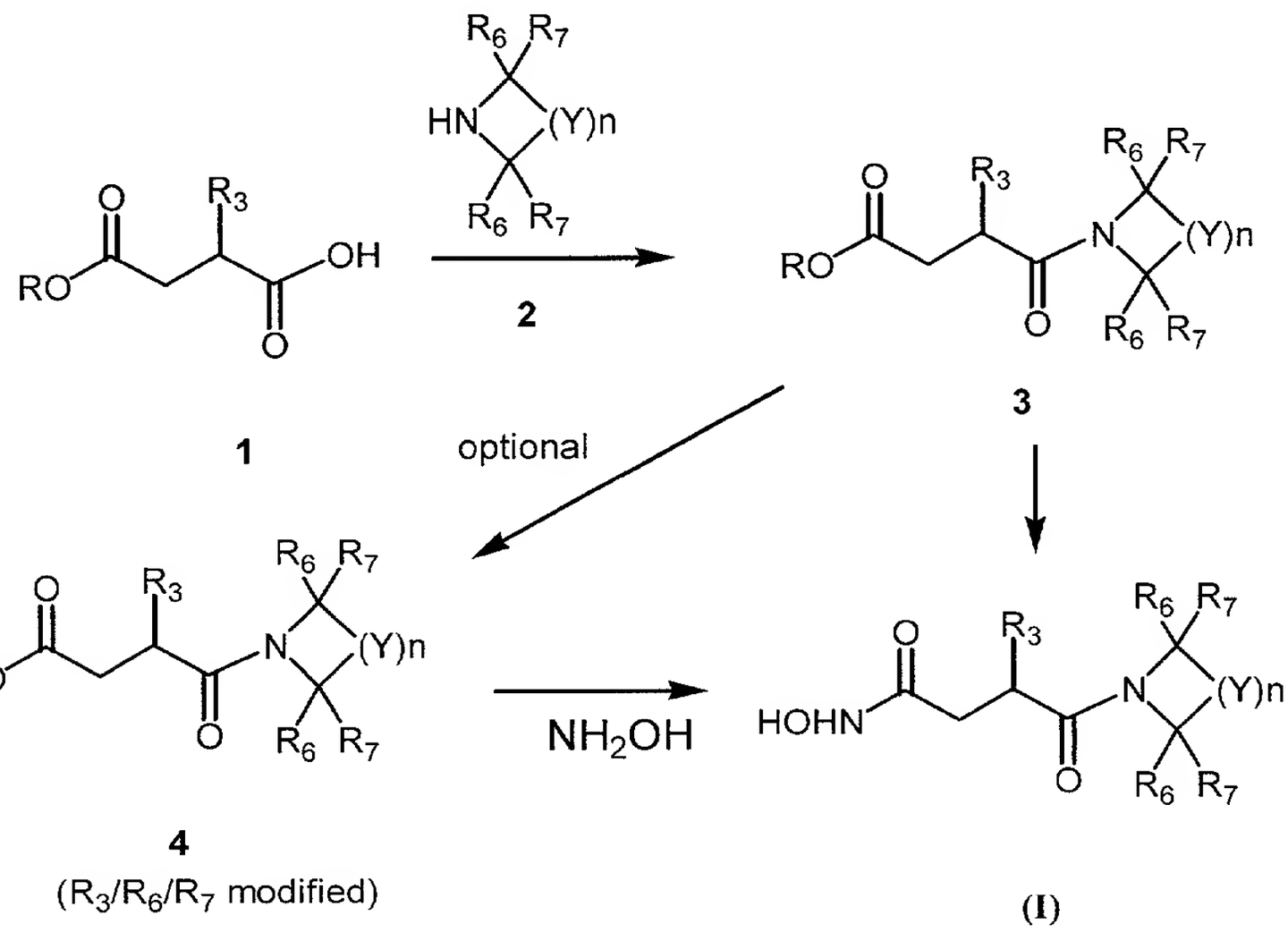
The starting materials and the intermediates of the reaction may be isolated and purified if desired using conventional techniques, including but not limited to filtration, distillation, crystallization, chromatography, and the like. Such materials may be characterized using conventional means, including physical constants and spectral data.

Preparation of compounds of Formula (I)

Compounds of Formula (I) can be prepared by methods well known in the art of organic chemistry. Representative synthetic procedures for preparing compounds of the present invention are illusted and described in detail below. For example, compounds of Formula (I) can be prepared as described in Schemes A -D below.

A compound of Formula (I) where R_1, R_2, and R_4 are hydrogen, and R_3, R_6, R_7, Y, and n are as defined in the Summary of the Invention can be prepared as described in Scheme A below.

Scheme A



Treatment of a solution of a *mono*-protected succinate of formula **1** where R is an alkyl group such as methyl, ethyl, and the like, and R_3 is as defined in the Summary of the Invention, with an N,N-dialkylamine of formula **2**, where R_6 and R_7

are as defined in the Summary of the Invention, provides a 3-aminocarbonyl-propionate derivative of formula **3**. The reaction is typically carried out in the presence of an inert, polar aprotic solvent (e.g. DMF, dioxane, etc.) in the presence of a non-nucleophilic base (e.g. triethylamine, diisopropylethylamine, etc.) and a coupling reagent (e.g. EDCI, PyBOP, DIC, etc.). The reaction is initially started at low temperature, such as 0 °C, and then allowed to warm to room temperature, and then stirred for several hours. Some compounds of formula **1** are commercially available. Others can be prepared by methods well known in the art. For example *mono*-methyl succinate, mono-4-methyl-2-(*R*)-methylsuccinate is available commercially, while *mono*-4-methyl-2-(*R*)-butylsuccinate as described in detail in Example 16 below.

Amines of formula **2** are commercially available or they can be prepared by methods well known in the art. For example, *N*, *N*-dialkylamines such as pyrrolidine, piperidine, piperazine, morpholine, thiomorpholine, homopiperidine, homopiperazine, proline *tert*-butyl ester, *L*-proline-2-methylamide, (*S*)-(+)-2-(methoxymethyl)-pyrrolidine, *L*-proline-*N*-methoxy-*N*-methylamide, (*S*)-2-(pyrrolidinylmethyl)-pyrrolidine, *L*-proline-*N*-morpholineamide, *L*-proline-*N,N*-dimethylamide, homoproline methyl ester, *L*-homoproline *tert*-butylester, 3-(*R*)- *tert*-butoxy-*L*-proline-O- *t*-butyl ester, pipecolinic acid, 1,2,3,4-tetrahydroquinoline, 1-hydroxyethylpiperazine, 2-hydroxyethylpiperidine, 3-hydroxypiperidine, 4-hydroxypiperidine, 4-hydroxyproline, *L*-tetrahydroisoquinoline *tert*-butyl ester, 3-(*N*-Boc-amino)pyrrolidine, and *N-Boc*-L-prolinol are commerically available. Other N,N-dialkylamines **2** such as 2-acetylaminomethylpyrrolidine can be prepared from *N-Boc-L*-prolinol as described in Example 16 below. *trans*-3-Acetoxy-*L*-proline *O*-*tert*-butyl ester can be prepared from Cbz protected trans-3-hydroxy-*L*-proline as described in Example 17 below which can then be converted to trans 3-hydroxy-*L*-proline O-*tert*-butyl ester, if desired, by hydrolysis of the acetoxy group in trans-3-acetoxy-*L*-proline O-*tert*-butyl ester as described in Example 17 below.

Also, it will be recognized by a person skilled in the art that if compound **1** and /or **2** have additional reactive groups, then they must be suitably protected prior to carrying out the coupling reaction. Examples of suitable protecting groups and their introduction and removal are described in T.W. Greene and G. M. Wuts, "*Protecting Groups in Organic Synthesis*" Third Ed., Wiley, New York, 1999 and references cited therein. For example, if R_6 or R_7 is a carboxyl group or a hydroxy group then it can

be protected as a *t*-butyl ester or benzyl ester or other suitable protecting group prior to the coupling reaction.

Compound **3** can optionally be converted to a compound of formula **4** where prior to converting it to a compound of Formula (I). This would be desirable if certain group(s) in compound **3**, e.g., R_3, R_6, and/or R_7 had to transformed to other group(s) within the scope of the invention prior to introducing the hydroxamate group in the molecule. For example, a compound of formula **3** where R_6 or R_7 is a *tert*-butoxyamino group, can be converted to a corresponding compound of formula **4** where R_6 or R_7 is an acetylamino group by first treating **3** with an acid such as diluted hydrochloric acid at ambient temperature to provide a corresponding compound of formula **3** where R_6 or R_7 is an amino group, followed by treatment with an acetylating agent such as acetic anhydride in the present of an organic base such as pyridine.

A compound of formula **3** where R_6 and\or R_7 is a hydroxy can be converted to a compound of formula **4** where R_6 and\or R_7 is a sulfonamido group (i.e., -$NHSO_2R_{15}$ where R_{15} is as defined in the Summary of the Invention) by first converting the hydroxy group into amino group, followed by treatment with a sulfonylating agent. A detailed description of this transformation is provided in Example 34 below.

A compound of formula **3** where R_6 and\or R_7 is a suitably protected carboxyl group can be converted to a compound of formula **4** where R_6 and\or R_7 is an aminocarbonyl group (i.e., -$CONHR_{14}$ or –$CONR_{14}R_{15}$ where R_{14} and R_{15} is as defined in the Summary of the Invention) by first deprotecting the carboxy group and then treating with an amine of formula -NHR_{14} or -$NR_{14}R_{15}$ (where R_{14} and R_{15} is as defined in the Summary of the Invention). Briefly, the reaction conditions for deprotecting of the carboxy group will depend on the nature of the protecting group. For example, if it is a benzyl ester, then treatment with hydrogen gas and an appropriate catalyst (e.g., 10 % palladium on carbon) will liberate the free carboxylic acid. The amination reaction is typically carried out in the presence of an inert, polar aprotic solvent (e.g. DMF, dioxane, etc.) with a non-nucleophilic base (e.g. triethylamine, diisopropylethylamine, etc.) and a coupling reagent (e.g. EDCI, PyBOP, DIC, etc.). The reaction is initially started at low temperature, such as 0 °C, and then allowed to warm to room temperature, and then stirred for several hours. Many amines of formulae NHR_{14} and $NHR_{14}R_{15}$ are available commercially, or can

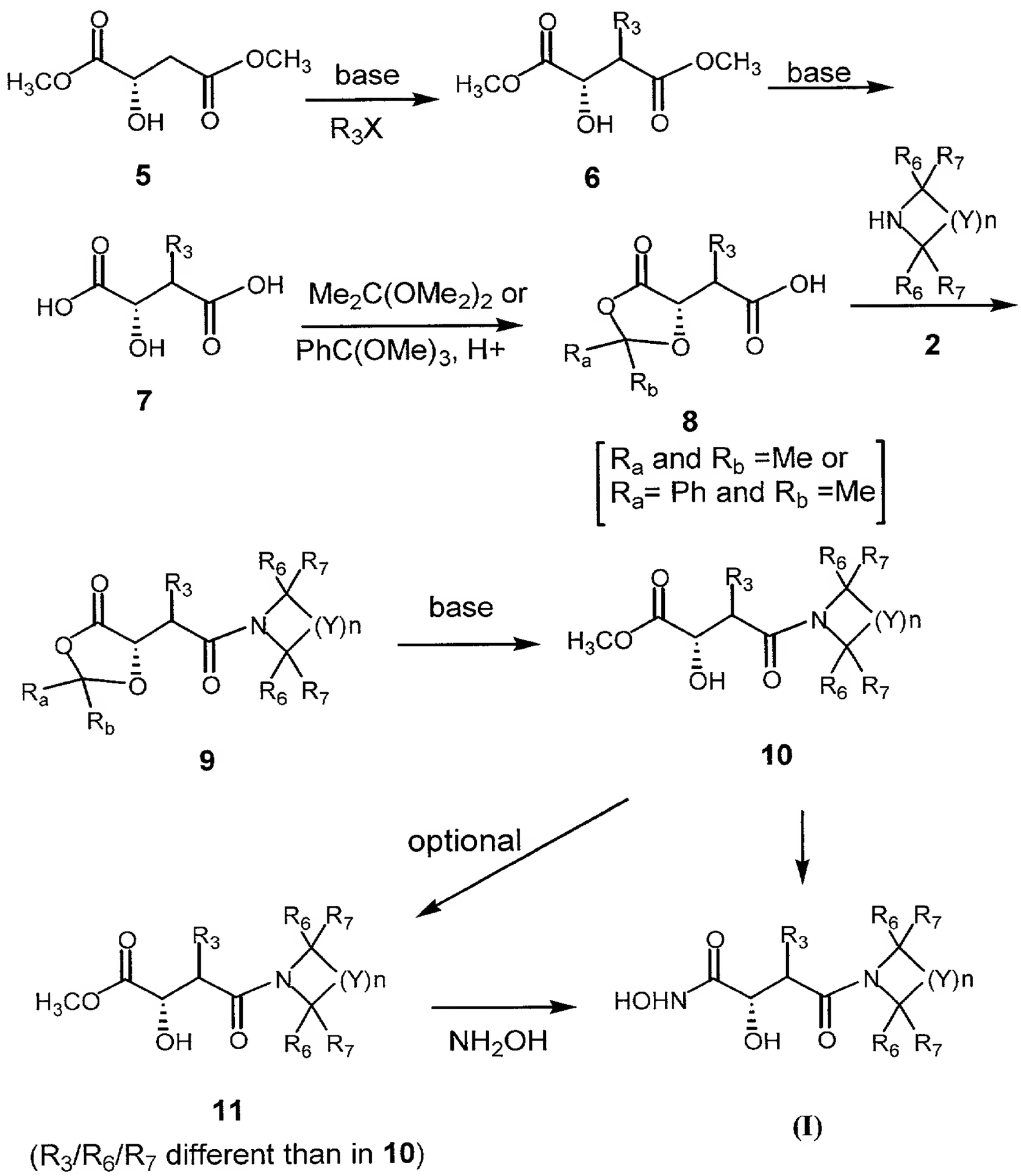
be readily prepared by methods well known in the art. For example, methylamine, aniline, 2-aminothiazole, etc., are commercially available. Others can be prepared, for example, *via* reductive amination of an aldehyde, or Fukuyama alkylation of a suitable nitroaryl sulfonamide followed by cleavage of the sulfonamide to liberate the desired amine.

Compound **3** or **4** is then converted to a hydroxamate compound of Formula (I) by treating it at 0 °C with aqueous 50 % hydroxylamine in a polar organic solvent such as dioxane and the like. After the reaction is complete the mixture is then purified by preparative reverse-phase (C18) HPLC to afford compound of Formula (I). If desirable, suitable O-protected hydroxylamine such as O-benzylhydroxyl-amine can also be used to give an O-protectedhydroxamate compound. Removal of the protecting group will provide a compound of Formula (I).

A compound of Formula (I) can be converted to other compounds of Formula (I) by methods well known in the art. Some such methods are described below. Compounds of Formula (I) containing a hydroxy group may be prepared by de-alkylation/benzylation of an alkyloxy/benzyloxy substituent; and those containing an acid group, by hydrolysis of an ester group. Similarly, a compound of Formula (I) having an alkenyl or alkynyl group can be prepared by reacting a corresponding compound of Formula (I) containing a bromine or iodine atom with trimethylsilylacetylene under the Castro-Stephens reaction conditions. Furthermore, a compound of Formula (I) containing an alkoxy group may be prepared by alkylation of hydroxy substituent. A compound of Formula (I) containing a carboxy group can be prepared by hydrolyzing an ester group in a corresponding compound of Formula (I) under acid hydrolysis reaction conditions. The resulting carboxy group can optionally be converted to an amido group, if desired, by first converting the carboxy group to an activated ester derivative *e.g.*, treating the carboxy compound with dicyclohexyl carbodiimide, DEAD and the like, followed by treatment with an amine. It will be recognized by a person skilled in the art that some of these transformations can be carried out prior to converting the compound of formula **5** to a compound of Formula (I).

A compound of Formula (I) where R_1 is hydroxy, R_2, and R_4 are hydrogen, and R_3, R_6, R_7, Y, and n are as defined in the Summary of the Invention can be prepared as described in Scheme B below.

Scheme B



Treatment of dimethyl malate **5** under strongly basic conditions with an appropriate alkylhalide R_3X (where R_3 is alkyl, alkenyl, alkynyl, substituted, heteroalkyl and X is halo such as chloro, bromo, or iodo) provides 2-substituted dimethyl malate **6**. The reaction is typically carried out in a polar aprotic solvent such as THF, and the base is typically lithium diisopropylamide (LDA). The reaction is initially carried out at a low temperature, preferably at about – 78 °C, and then

allowed to slowly warm to room temperature. The reaction is then stirred for several hours. The reaction is typically higher yielding when R_3X is an allylic halide. After the alkylation is complete the resulting olefin can be reduced, if desired, to provide a compound of formula **6** where R_3 is alkyl. The typically reduction procedure involves a suspension of **6** and a catalyst (e.g., 10 % palladium on carbon) in a solvent such as ethylacetate and would be stirred under a hydrogen atmosphere for several hours to afford the corresponding compound of formula **6** where R_3 is alkyl. Many compounds of formula R_3X are commercially available or they can be prepared by methods well known in the art. For example, iodomethane, benzylbromide, crotylbromide, allylbromide, vinylbromide are commercially available. Others can be prepared from the corresponding alcohol by first activating the hydroxy group as a *p*-toluenesulfonate ester (tosyl ester), followed by tosylate displaced with a halide ion in a modified Finkelstein procedure to afford an alkylhalide as described in working examples below.

Treatment of **6** with a base affords a malic acid derivative of formula **7**. The base can be an inorganic base such as lithium hydroxide or potassium hydroxide, and is most preferably sodium hydroxide. This reaction is usually performed in a polar, protic solvent such as methanol. Treatment of **7** with an orthoacetate, such as trimethylorthobenzoate, in the presence of an acidic catalyst affords an orthoester **8** (R_a is -Ph and R_b is –OMe). This reaction is ideally performed with a co-solvent, preferably in a mixture of toluene. The reaction is ideally performed at a higher temperature, most preferably at 110 °C. The catalyst is typically a sulfonic acid, such as *p*-toluenesulfonic acid, or most preferably camphorsulfonic acid.

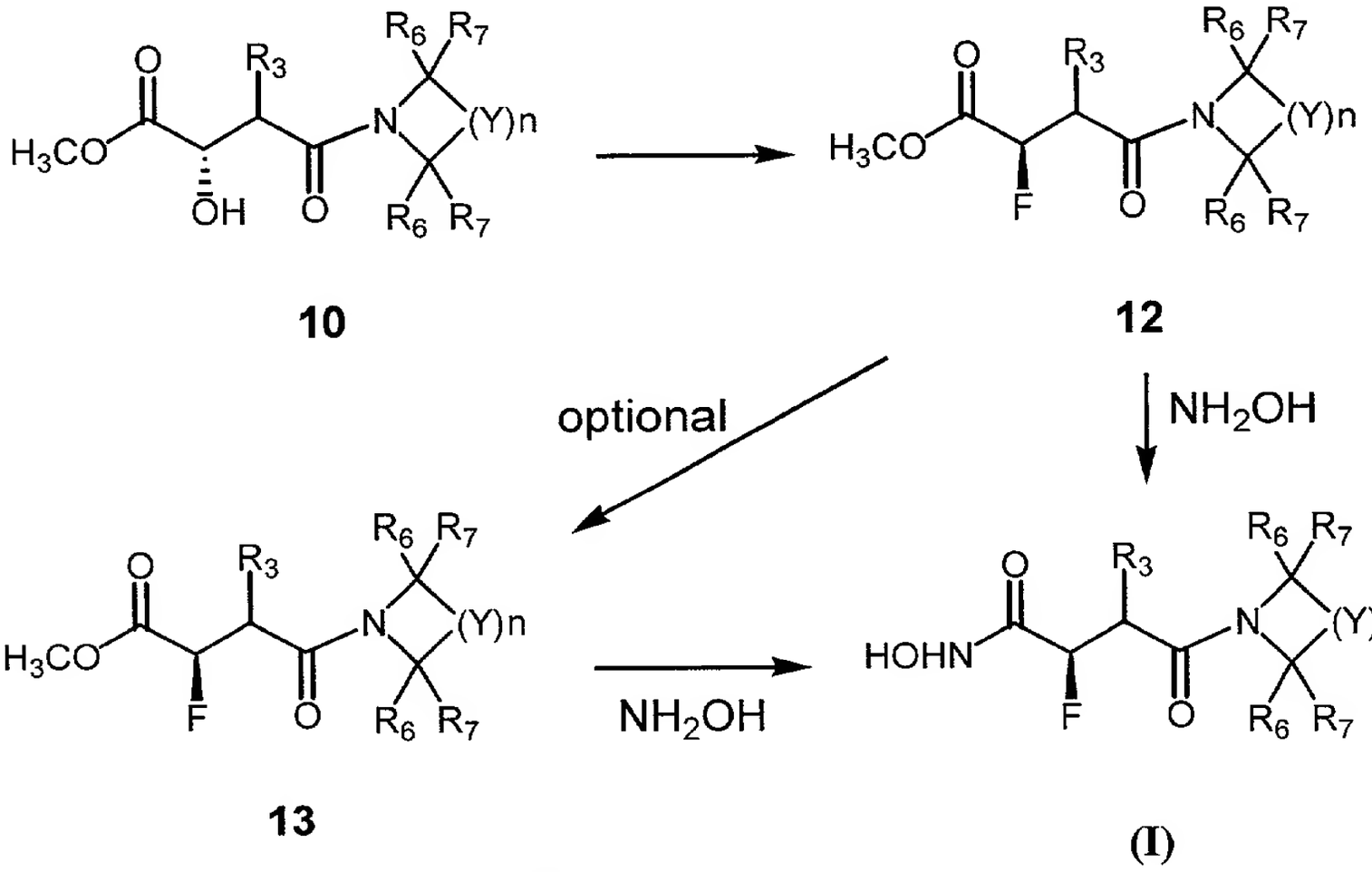
Alternatively, treatment of **7** with 2,2-dimethoxypropane in the presence of *p*-toluenesulfonic acie provides an acetonide of formula **8** where R_a and R_b are methyl.

Treatment of the orthoester or acetonide **8** with a dialkylamine of formula **2** under the reaction conditions described in Scheme A provides a compound of formula **9** which upon treatment with a base, preferably the salt of an alcohol, and more preferably sodium methoxide in an alcoholic solvent then provides a 2-hydroxy-3-aminocarbonyl-propionate derivative of formula **10**.

Compound **10** is then optionally converted to a compound of formula **11** for reasons discussed in Scheme A such as derivatizing the R_3, R_6 and/or R_7 groups prior to converting it to a compound of Formula (I). Alternatively, compound **10** it can be directly converted to a compound of Formula (I) as described in Scheme A above.

It will be recognized by a person skilled in the art that the hydroxy group in compound **10** can be replaced by various other R_1 groups as defined in the Summary of the Invention prior to converting it to a compound of Formula (I). Some representative examples are discussed below:

(i) the hydroxy group in compound **10** can be replaced by a fluoro group prior to converting it to a compound of Formula (I) as shown below.



The hydroxyl group at the C2 carbon in compound **10** can be replaced by a fluoro group by first converting the hydroxyl group into an active ester followed by displaced with fluorine to afford compound **12**. The reaction is performed in a halogenated solvent, such as dichloromethane (DCM), in the presence of an organic base, such as pyridine. The alcohol is typically activated as a sulfonate ester, preferably the trifluoromethane-sulfonate. This esterification reaction is typically carried out at a low temperature, preferably about –20 °C. The active ester is then reacted with a fluoride ion, typically derived from tris(dimethylamino)sulfur-(trimethylsilyl)difluoride (TAS-F). This reaction is also carried out at a low temperature, preferably at about –50 °C, and then slowly allowed to warm to ambient temperature. Compound **12** is then converted to a compound of Formula (I) either directly or through compound **13** as described above. A detailed description of this

procedure is provided in Example 6 below. It will be noted that the stereochemistry at the C2 carbon atom is inverted during this transformation.

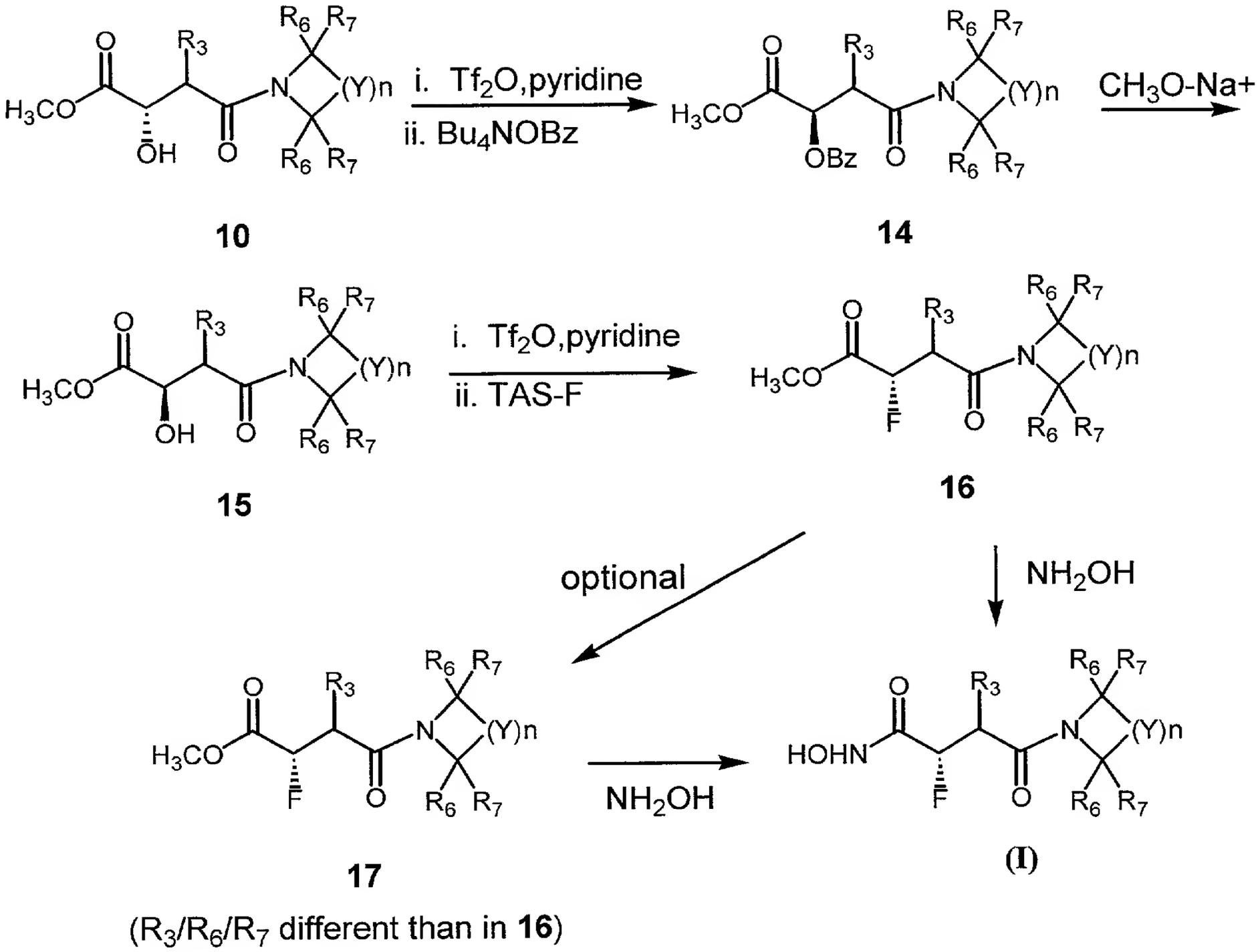
(ii) the hydroxy group in compound **10** can be converted to an alkoxy under alkylation reaction conditions such as treatment of **10** with an alkyl halide such as methyl iodide, ethyl iodide, benzyl bromide, and the like, in the presence of a strong base such as sodium hydride and in a polar solvent such as dimethylformamide. Detailed description of this procedure is provided in Example 45 below.

(iii) the hydroxy group in compound **10** can be converted to benzoyloxy group by first converting it into an activated ester such as a sulfonate ester, preferably the trifluoromethanesulfonate, followed by treatment with tetrabutyl ammomium benzoate. Detailed description of this procedure is provided in Example 47 below.

(iii) the hydroxy group in compound **10** can be converted to thiol group by first converting it into an activated ester such as a sulfonate ester, preferably the trifluoromethanesulfonate, followed by treatment potassium thioacetate. Detailed description of this procedure is provided in Example 48 below.

(iv) the hydroxy group in compound **10** can be converted to an azido or amino group or it's derivatives by first converting it into an activated ester such as a sulfonate ester, preferably the trifluoromethanesulfonate, followed by treatment with sodium azide. The azide group can optionally reducted under catalytic hydrogenation reaction conditions to give an amino group which can be further derivatized by methods well known in the art. Detailed description of this procedure is provided in Example 49 and 34 below.

(vi) the maintainence of the stereochemistry at the carbon atom carrying the hydroxy group in compound **10**, the C2 carbon, can be achieved by carrying out double inversion as illustrated and described below.



The hydroxyl at the C-2 carbon of intermediate **10** is converted to an active ester as described above in (i) above. Nucleophilic substitution with a variety of nucleophiles such as acetate anion, or more preferably, tetrabutylammonium benzoate, provides intermediate **14**. This reaction proceeds in a hydrocarbon solvent, preferably in toluene. One skilled in the art will understand that the above nucleophilic displacement reaction results in an inversion of stereochemistry at the C-2 position.

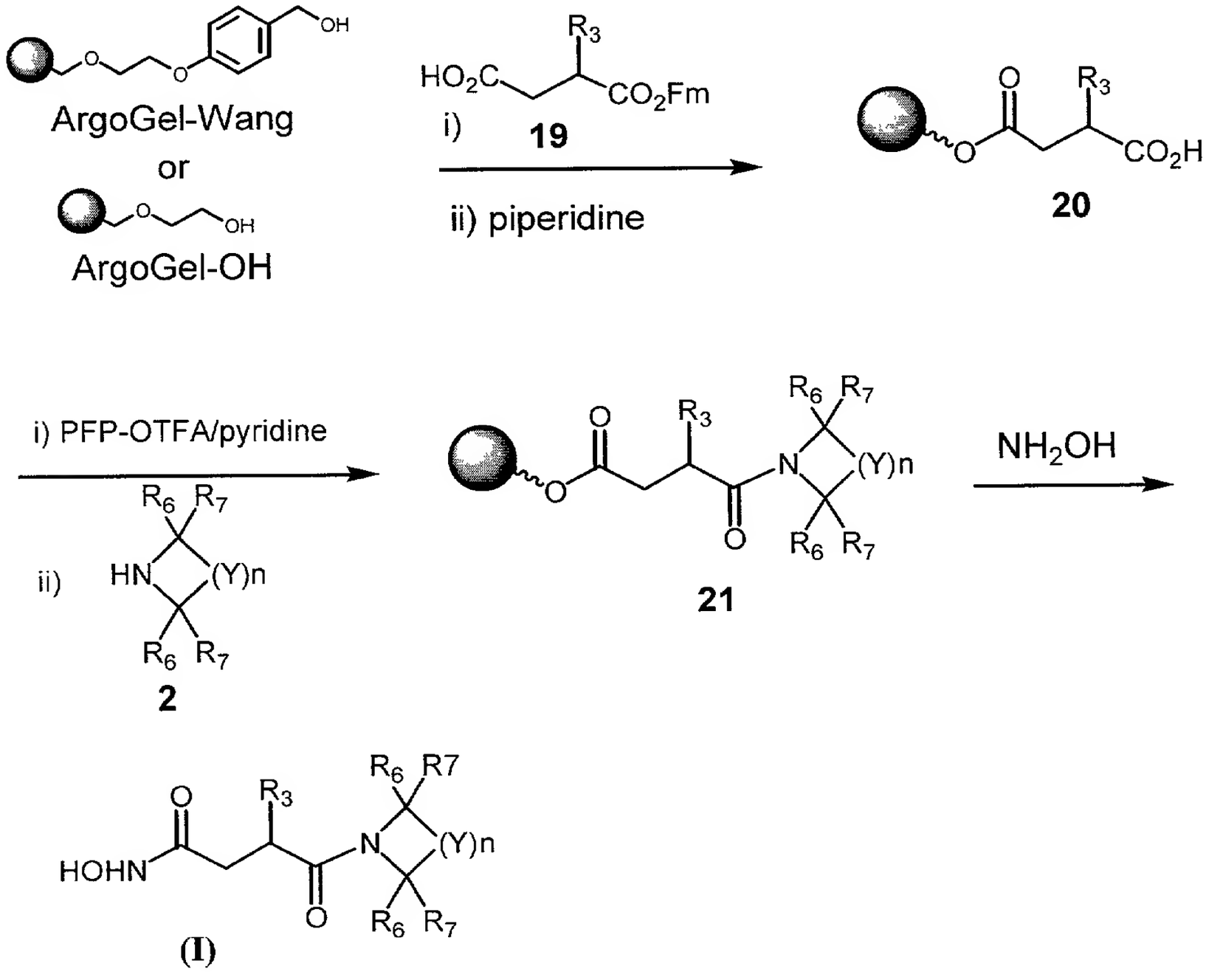
Compound **14** is treated with a base to afford hydroxy derivative **15**. This base is preferably the salt of an alcohol such as sodium methoxide, sodium ethoxide and the like, and more preferably sodium methoxide. The reaction proceeds in an alcoholic solvent such as methanol, ethanol and the like, most preferably in methanol.

Compound **15** is re-activated as a sulfonate ester, preferably a trifluoromethane sulfonate as described above and then treated with a fluorination reagent, preferably TAS-F, to afford the corresponding fluoro intermediate **16** which has the same stereochemistry at the C-2 carbon as in intermediate **10**.

Compound **16 or 17** is then converted to a compound of Formula (I) as discussed above.

A compound of Formula (I) can also be prepared as illustrated in Scheme C below.

Scheme C

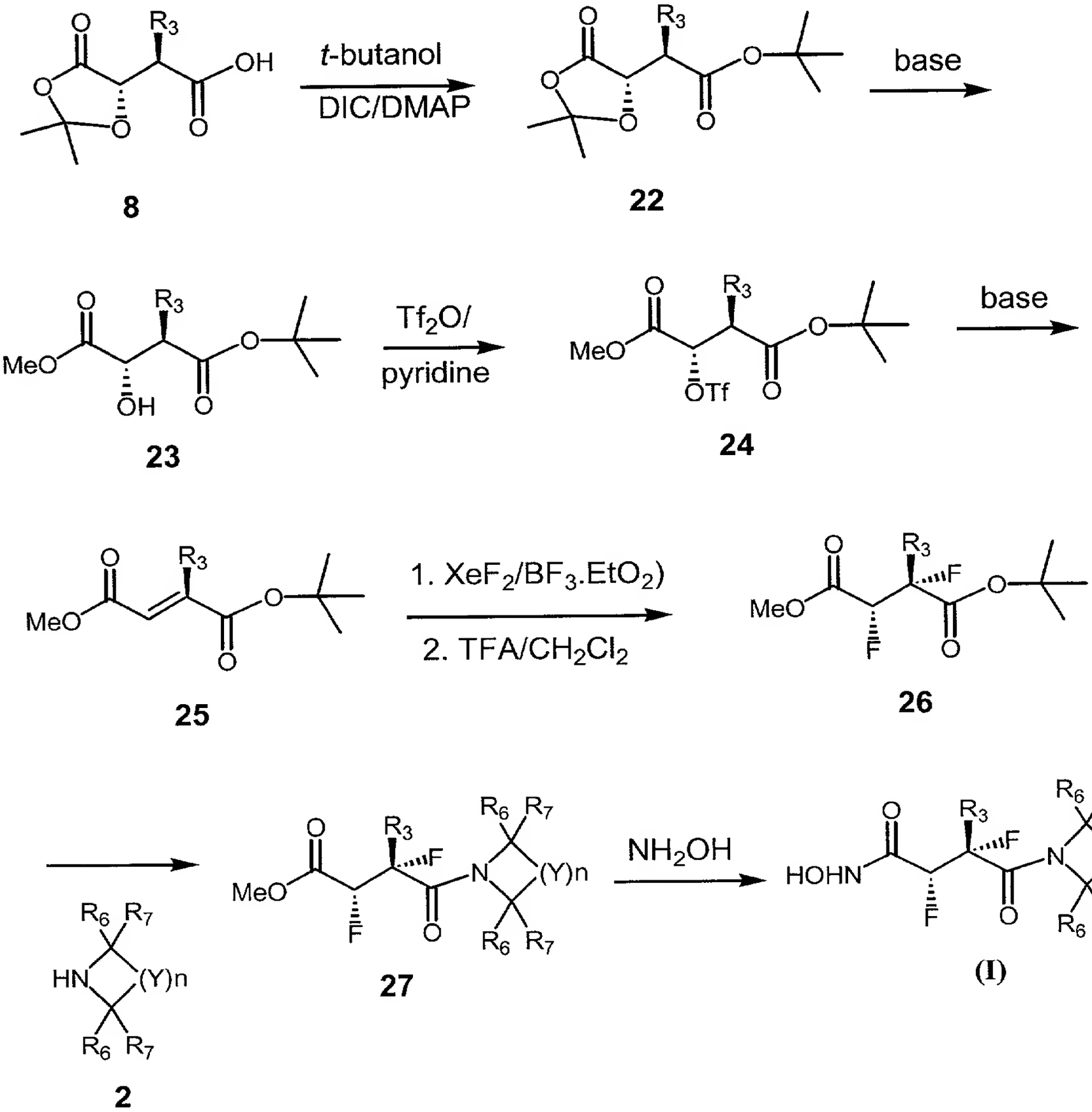


Treatment of a suspension of ArgoGel-Wang or ArgoGel-OH resin with an Fm-protected succinic acid of formula **19** (wherein R_3 is as defined in the Summary of the Invention) in the presence of a coupling agent such as di-isopropylazodicarboxylate and triphenylphosphine, followed by treatment with piperidine provides a resin bound Fm-protected succinic acid **20**. The coupling reaction is carried out in a polar solvent such as dichloromethane in the presence of a base such as dimethylaminopyridine. The reaction is typically carried out at ambient temperature. Treatment of **20** with PFP-OTFA and pyridine, followed by treatment with an amine **2** then provides resin bound 3-aminocarbonylpropionate **21**. The reaction is carried out

in the presence of a non-nucleophilic base such as pyridine, diethylisopropylamine, 2,4,6-collidine, and the like. The reaction is typically carried out at ambient temperature. Treatment of **21** with hydroxylamine then provides a compound of Formula (I).

A compound of Formula **(I)** where R_1 & R_2 are fluoro and R_2, R_3, R_6, R_7, Y and n are as defined in summary of the invention can be prepared as illustrated in Scheme D below.

Scheme D



Treatment of a compound of formula **8** with an alcohol such as *tert*-butanol in the presence of a suitable coupling agent such as DIC and a base such as DMAP provides the corresponding *tert*-butyl ester of formula **22**. Treatment of **22** with a base such as sodium methoxide in methanol provides 2-hydroxysuccinate derivative of formula **23**. Compound **23** is then converted to a trifluoromethanesulfonate ester derivative **24** using triflic anhydride in the presence of a base such as triethyamine, pyridine and the like. Treatment of **24** with a base such as triethylamine provides a maleic acid derivative of formula **25** which upon reaction with xenon difluoride in the presence of boron trifluoride etherate provides a 2,3-difluorosuccinate derivative. Removal of the tert-butyl group with trifluoroacetic acid provides the corresponding succinic acid derivative 26 which is then converted to a compound of Formula (I) as described above.

Administration, Utility and Testing

Administration and Pharmaceutical Composition

The present invention also provides pharmaceutical compositions which comprise a bioactive hydroxamic acid compound or derivative, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier. The compositions of the invention include those in a form adapted for oral, topical or parenteral use and can be used for the treatment of bacterial infection in animals, preferably mammals, more preferably humans.

The antibiotic compounds, also referred to herein as antimicrobial compounds, according to the invention can be formulated for administration in any convenient way for use in human or veterinary medicine, by analogy with other antibiotics. Such methods are known in the art (*see*, e.g., Remington's Pharmaceutical Sciences, Easton, PA: Mack Publishing Co.) and are not described in detail herein.

The composition can be formulated for administration by any route known in the art, such as subdermal, inhalation, oral, topical or parenteral. The compositions can be in any form known in the art, including but not limited to tablets, capsules, powders, granules, lozenges, creams or liquid preparations, such as oral or sterile parenteral solutions or suspensions. The compounds can also be administered in liposome formulations. The compounds can also be administered as prodrugs, where the prodrug administered undergoes biotransformation in the treated mammal to a form which is biologically active.

The topical formulations of the present invention can be presented as, for instance, ointments, creams or lotions, solutions, salves, emulsions, plasters, eye ointments and eye or ear drops, impregnated dressings and aerosols, and can contain appropriate conventional additives such as preservatives, solvents to assist drug penetration and emollients in ointments and creams.

The formulations can also contain compatible conventional carriers, such as cream or ointment bases and ethanol or oleyl alcohol for lotions. Such carriers can be present, for example, from about 1% up to about 99% of the formulation. For example, they can form up to about 80% of the formulation.

Tablets and capsules for oral administration can be in unit dose presentation form, and can contain conventional excipients such as binding agents, for example syrup, acacia, gelatin, sorbitol, tragacanth, or polyvinylpyrollidone; fillers, for example lactose, sugar, maize-starch, calcium phosphate, sorbitol or glycine; tabletting lubricants, for example magnesium stearate, talc, polyethylene glycol or silica; disintegrants, for example potato starch; or acceptable wetting agents such as sodium lauryl sulphate. The tablets can be coated according to methods well known in standard pharmaceutical practice.

Oral liquid preparations can be in the form of, for example, aqueous or oily suspensions, solutions, emulsions, syrups or elixirs, or can be presented as a dry product for reconstitution with water or another suitable vehicle before use. Such liquid preparations can contain conventional additives, such as suspending agents, for example sorbitol, methyl cellulose, glucose syrup, gelatin, hydroxyethyl cellulose, carboxymethyl cellulose, aluminium stearate gel or hydrogenated edible fats; emulsifying agents, for example lecithin, sorbitan monooleate, or acacia; non-aqueous vehicles (which can include edible oils), for example almond oil, oily esters such as glycerine, propylene glycol, or ethyl alcohol; preservatives, for example methyl or propyl p-hydroxybenzoate or sorbic acid, and, if desired, conventional flavoring or coloring agents.

For parenteral administration, fluid unit dosage forms are prepared utilizing the compound and a sterile vehicle, water being preferred. The compound, depending on the vehicle and concentration used, can be either suspended or dissolved in the vehicle or other suitable solvent. In preparing solutions, the compound can be dissolved in water for injection and filter sterilized before filling into a suitable vial or ampoule and sealing. Advantageously, agents such as a local anesthetic preservative

and buffering agents can be dissolved in the vehicle. To enhance the stability, the composition can be frozen after filling into the vial and the water removed under vacuum. The dry lyophilized powder is then sealed in the vial and an accompanying vial of water for injection can be supplied to reconstitute the liquid prior to use. Parenteral suspensions are prepared in substantially the same manner except that the compound is suspended in the vehicle instead of being dissolved and sterilization cannot be accomplished by filtration. The compound can be sterilized by exposure to ethylene oxide before suspending in the sterile vehicle. Advantageously, a surfactant or wetting agent is included in the composition to facilitate uniform distribution of the compound.

The compositions can contain, for example, from about 0.1% by weight to about 99% by weight, e.g., from about 10-60% by weight, of the active material, depending on the method of administration. Where the compositions comprise dosage units, each unit will contain, for example, from about 1-500 mg of the active ingredient. The dosage as employed for adult human treatment will range, for example, from about 1 to 3000 mg per day, for instance 1500 mg per day depending on the route and frequency of administration. Such a dosage corresponds to about 0.015 to 50 mg/kg per day. Suitably the dosage is, for example, from about 5 to 20 mg/kg per day.

Utility

The hydroxamate compounds of the present invention can be used for the treatment or prevention of infectious disorders caused by a variety of bacterial or prokaryotic organisms. Examples include Gram positive and Gram negative aerobic and anaerobic bacteria, including *Staphylococci*, for example *S. aureus* and *S. epidermidis*; *Enterococci*, for example *E. faecalis* and *E. faecium*; *Streptococci*, for example *S. pneumoniae*; *Haemophilus*, for example *H. influenza*; *Moraxella*, for example *M. catarrhalis*; and *Escherichia*, for example *E. coli*. Other examples include *Mycobacteria*, for example *M. tuberculosis*; intercellular microbes, for example *Chlamydia* and *Rickettsiae*; and *Mycoplasma*, for example *M. pneumoniae*.

In one embodiment, compositions, for treating or preventing infectious disorders are provided, comprising a hydroxamic acid compound or derivative as disclosed herein in combination with a pharmaceutically acceptable carrier.

In another embodiment, there is provided a dosage amount of a hydroxamic acid compound or derivative as disclosed herein in an effective amount for the treatment, prevention or alleviation of a disorder, such as an infectious disorder. Hydroxamic acid compounds or derivatives can be screened for activity against different microbial agents and appropriate dosages can be determined using methods available in the art.

The compounds can be used to treat a subject to treat, prevent, or reduce the severity of an infection. Subjects include animals, plants, blood products, cultures and surfaces such as those of medical or research equipment, such as glass, needles, surgical equipment and tubing, and objects intended for temporary or permanent implantation into an organism. Treating a subject includes, but is not limited to, preventing, reducing, or eliminating the clinical symptoms caused by an infection of a subject by a microorganism; preventing, reducing, or eliminating an infection of a subject by a microorganism; or preventing, reducing, or eliminating contamination of a subject by a microorganism. The microorganism involved is preferably a prokaryote, more preferably a bacterium.

In one embodiment, methods of treating or preventing an infectious disorder in a subject, such as a human or other animal subject, are provided, by administering an effective amount of a hydroxamic acid compound or derivative as disclosed herein to the subject. In one embodiment, the compound is administered in a pharmaceutically acceptable form optionally in a pharmaceutically acceptable carrier. As used herein, an "infectious disorder" is any disorder characterized by the presence of a microbial infection, such as the presence of bacteria. Such infectious disorders include, for example central nervous system infections, external ear infections, infections of the middle ear, such as acute otitis media, infections of the cranial sinuses, eye infections, infections of the oral cavity, such as infections of the teeth, gums and mucosa, upper respiratory tract infections, lower respiratory tract infections, genitourinary infections, gastrointestinal infections, gynecological infections, septicemia, bone and joint infections, skin and skin structure infections, bacterial endocarditis, burns, antibacterial prophylaxis of surgery, and antibacterial prophylaxis in immunosuppressed patients, such as patients receiving cancer chemotherapy, or organ transplant patients. The compounds and compositions comprising the compounds can be administered by routes such as topically, locally or systemically. Systemic application includes any method of introducing the compound into the tissues of the

body, *e.g.*, intrathecal, epidural, intramuscular, transdermal, intravenous, intraperitoneal, subcutaneous, sublingual, nasal, vaginal, rectal, and oral administration. The specific dosage of antimicrobial to be administered, as well as the duration of treatment, can be adjusted as needed.

Additionally, the compounds of this invention can also be used to prepare a composition in an inert diluent which is useful in inhibiting bacterial growth. An "inert diluent" means an excipient that is useful in preparing a composition that is generally safe, non-toxic and neither biologically nor otherwise undesirable.

Representative pharmaceutical formulations containing a compound of Formula (I) are described below.

Testing

The ability of the compounds of this invention to inhibit peptide deformylase was measured by *in vitro* assay described in detail in Biological Example below. The antimicrobial activity of the compounds of this invention was tested as described in detail in Biological Example 2 below. The selective inhibition of PDF compared to MMP-7 (Matrilysin) by the compounds of this invention was tested as described in detail in Biological Example 3 below.

EXAMPLES

The following preparations and examples are given to enable those skilled in the art to more clearly understand and to practice the present invention. They should not be considered as limiting the scope of the invention, but merely as being illustrative and representative thereof.

Abbreviations

The following abbreviations are used:

AcOH, HOAc = acetic acid

Ac_2O = acetic anhydride

BOC, Boc = t-butyloxycarbonyl

DCC = dicyclohexylcarbodiimide

DCM = dichloromethane

DIC = diisopropylcarbodiimide

DIAD = diisopropylazodicarboxylate

DIEA = diisopropylethylamine

DMF = dimethylformamide

EDC = N-(3-Dimethylaminopropyl)-N'-ethylcarbodiimide

Et = ethyl

EtOAc = ethyl acetate

Fmoc, FMOC = 9-fluorenylmethyloxycarbonyl

HATU = O-(7-aza-benzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate

HBTU = O-(benzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate

HHMPA = (4-hydroxymethyl-3-methoxyphenoxy)-alkanoic acid

HMP resin = hydroxymethylphenoxy resin

HOAt = 1-hydroxy-7-azabenzotriazole

HOBt = 1-hydroxybenzotriazole

Me = methyl

Mem = methoxy ethoxy methyl ether

MeOH = methanol

MMP = matrix metalloproteinase

Mom = methoxy methyl ether

NMM = N-methyl morpholine

NPEOC = 4-nitrophenethyloxycarbonyl

NPEOM = 4-nitrophenethylmethyloxycarbonyl

NVOC = 6-nitroveratryloxycarbonyl

NVOM = nitroveratryloxymethyl ether

PEG-PS resins or PS-PEG resin = polyethylene glycol-polystyrene graft copolymer resins

PFP-OTFA = pentafluorophenyl trifluoroacetate

PyBOP = benzotriazole-1-yl-oxy-tris-pyrrolidinophosphonium hexafluorophosphate

PyBROP = bromotripyrrolidinophosphonium hexafluorophosphate

RT = room temperature

TBP = tributylphosphate

TBS, TBDIMS = t-butyldimethylsilyl

tBu = t-butyl

TES = triethylsilane

TFA = trifluoroacetic acid

TGS resin = TENTAGEL S resin

TGS NH_2 resin = TENTAGEL S NH_2 resin

THF = tetrahydrofuran

THP = 2-tetrahydropyranyl

TMAD = N,N,N',N'-tetramethylazodicarboxamide (1,1'-Azobis(N,N-dimethylformamide))

TMOF = trimethylorthoformate

TPP = triphenyl phosphine

TsCl = tosyl chloride

TsOH = toluenesulfonic acid

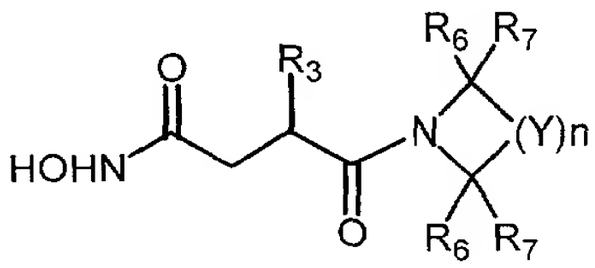
Trt = trityl

SYNTHETIC EXAMPLES

GENERAL PROCEDURE A

Synthesis of N-hydroxy-3-aminocarbonylpropionamide

(*following Scheme A*)



Step 1

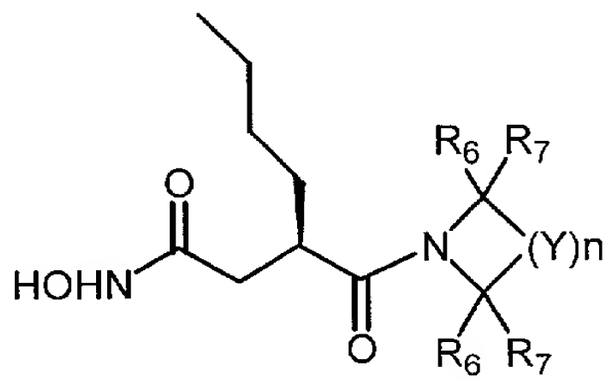
To a solution of mono-protected succinate *e.g., mono*-4-methyl 2-(*R*)-butylsuccinic acid **1** (1 mmol) in DMF was added dialkylamine **2** (1 mmol), DIEA (0.4 mL, 2.3 mmol), and an activating reagent (*e.g.* EDC, PyBOP, DIC, DCC, etc.; 1 mmol). The mixture was stirred overnight, then diluted with ethyl acetate and washed with aqueous HCl (1 N), water, saturated sodium bicarbonate, brine, and then dried (Na_2SO_4). The filtrate was concentrated and then purified on silica gel (Merck 60; ethyl acetate/hexane) to afford 3-aminocarbonylpropionate **3**.

Step 2

3-Aminocarbonylpropionate **3** (0.1 mmol) was treated with dioxane (1 mL) and hydroxylamine (50% in water, 2 mL) for 1 to 3 days, and then can be purified by preparative reverse-phase (C18) HPLC to afford the desired N-hydroxy-3-aminocarbonylpropionamide.

GENERAL PROCEDURE B

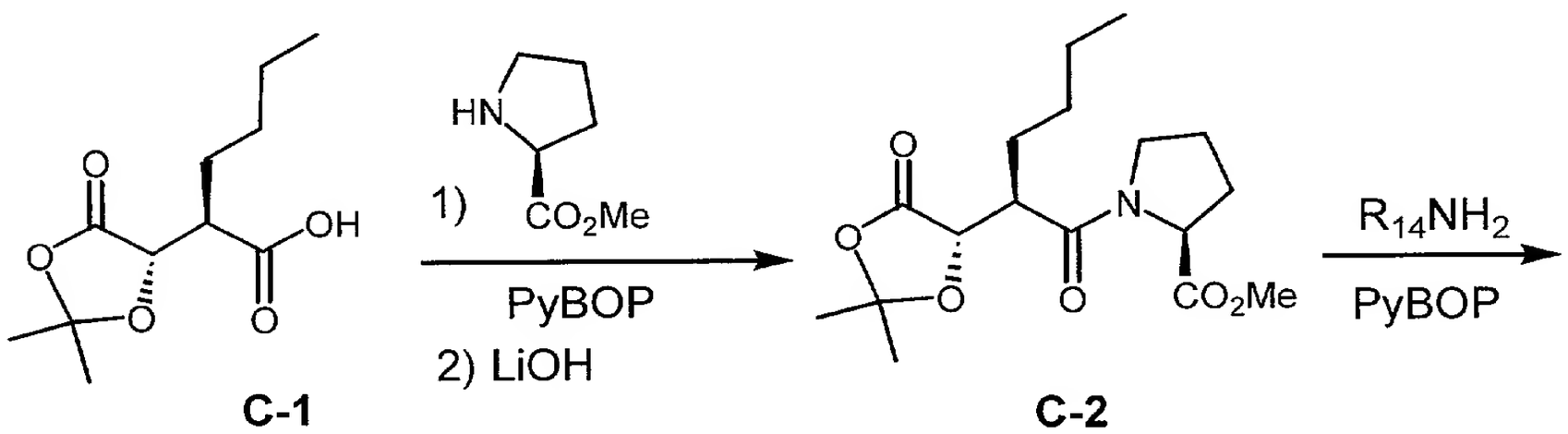
Synthesis of N-hydroxy-3-(*R*)-*n*-butyl-3-aminocarbonylpropionamide—
Alternate method

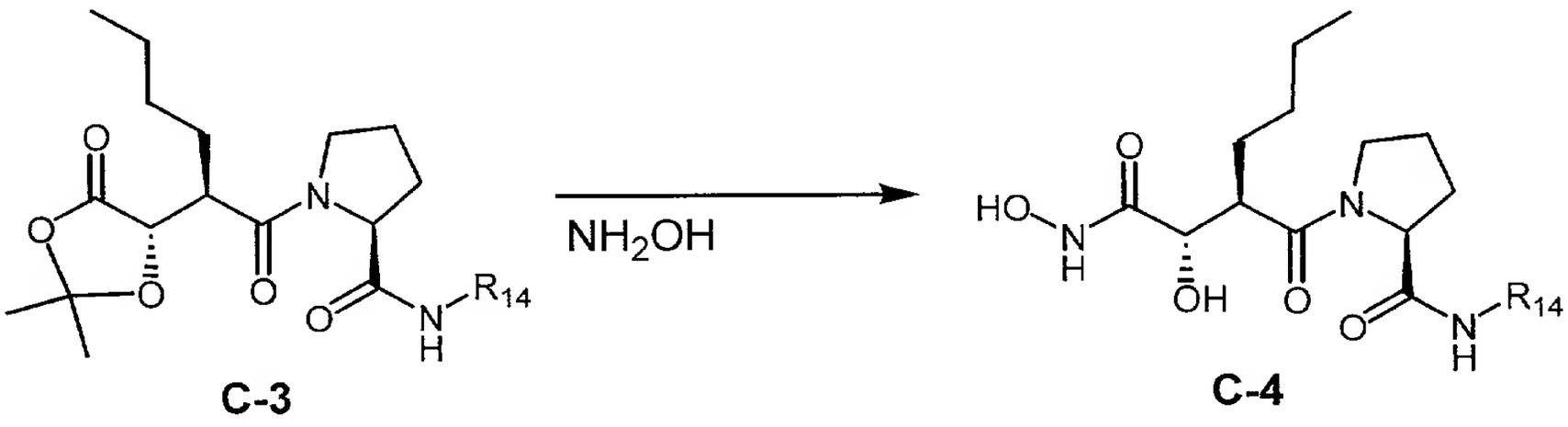


To *mono*-4-methyl 2-(*R*)-butylsuccinic acid (0.2 mmol) in dioxane (1 mL) was added amine **2** (0.2 mmol), DIEA (0.4 mmol) and an activating reagent (e.g. EDC, PyBOP, DIC, DCC, etc.; 0.2 mmol); and the mixture was stirred for 2 h. Aqueous 50% hydroxylamine was added (1.5 mL) and the mixture was stirred an additional 1-2 days. The reaction mixture can then be purified by preparative reverse-phase (C18) HPLC to afford N-hydroxy-3-(*R*)-*n*-butyl-3-aminocarbonylpropionamide.

GENERAL PROCEDURE C

Synthesis of N-hydroxy-3-(*R*)-*n*-butyl-3-[2-(*S*)-aminocarbonylpyrrolidin-1-ylcarbonyl)-2-(*S*)-hydroxypropionamide





Step 1

To 2-(2,2-dimethyl-4-oxo-1,3-dioxolan-5-yl)hexanoic acid **C-1** (prepared in four steps from dimethyl malate; see Example 21 for details) in DMF was added proline O-methyl ester, DIEA and HATU and the solution stirred 4 hours. Standard aqueous workup afforded the desired amide, which was dissolved in methanol and treated with lithium hydroxide to yield 1-(2,2-dimethyl-4-oxo-1,3-dioxolan-5-yl)-1-(2-(S)-carboxypyrrolidin-1-ylcarbonyl)pentane **C-2**.

Step 2

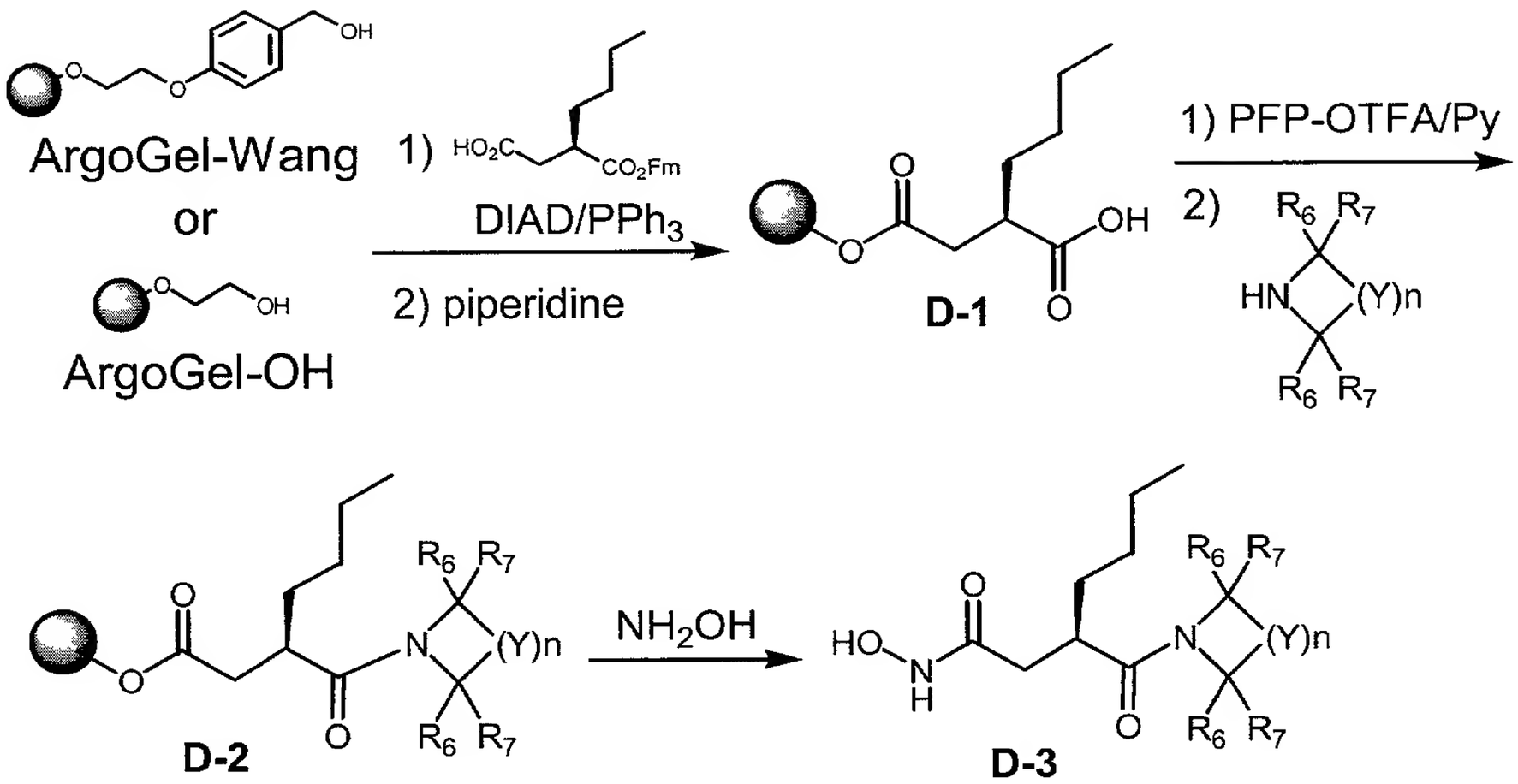
To 1-(2,2-dimethyl-4-oxo-1,3-dioxolan-5-yl)-1-(2-(S)-carboxypyrrolidin-1-ylcarbonyl)pentane **C-2** in DMF was added an amine $R_{14}NH_2$, DIEA and HATU and the solution stirred for 2 h. Aqueous workup followed by silica gel chromatography afforded 1-(2,2-dimethyl-4-oxo-1,3-dioxolan-5-yl)-1-(2-(S)-aminocarbonylpyrrolidin-1-ylcarbonyl)pentane **C-3**.

Step 3

To 1-(2,2-dimethyl-4-oxo-1,3-dioxolan-5-yl)-1-(2-(*S*)-aminocarbonyl-pyrrolidin-1-ylcarbonyl)pentane **C-3** in dioxane was treated with 50 % aqueous hydroxylamine for 4 h. The reaction mixture was then purified by preparative reverse-phase (C18) HPLC to afford N-hydroxy-3-(*R*)-*n*-butyl-3-[2-(*S*)-aminocarbonylpyrrolidin-1-ylcarbonyl)-2-(*S*)-hydroxypropionamide **C-4**.

GENERAL PROCEDURE D

Synthesis of N-hydroxy-3-(*R*)-*n*-butyl-3-[2-(S)-aminocarbonylpyrrolidin-1-yl-carbonyl)propionamide
(*following Scheme C*)



Step 1

To ArgoGel resin (20 g) solvated in DCM was added 2-(*R*)-*n*-butylsuccinate 1-(9-fluorenyl) ester (10.0 g, 23.2 mmol), diisopropylazodicarboxylate (DIAD; 4.8 mL, 24.3 mmol) and triphenylphosphine (PPh_3, 6.38 g, 24.3 mmol); the reaction mixture was shaken for 6 h. The resin is filtered and was washed with DCM (3x), MeOH (3 x) and DMF (3 x). A solution of piperidine (40 mL, 10% in DMF) was added and the resin mixture is shaken for 3 h. The resin was filtered and then washed sequentially with DMF (3x), DCM (2x), MeOH (2x) and DMF (3x) to afford intermediate **D-1**.

Step 2

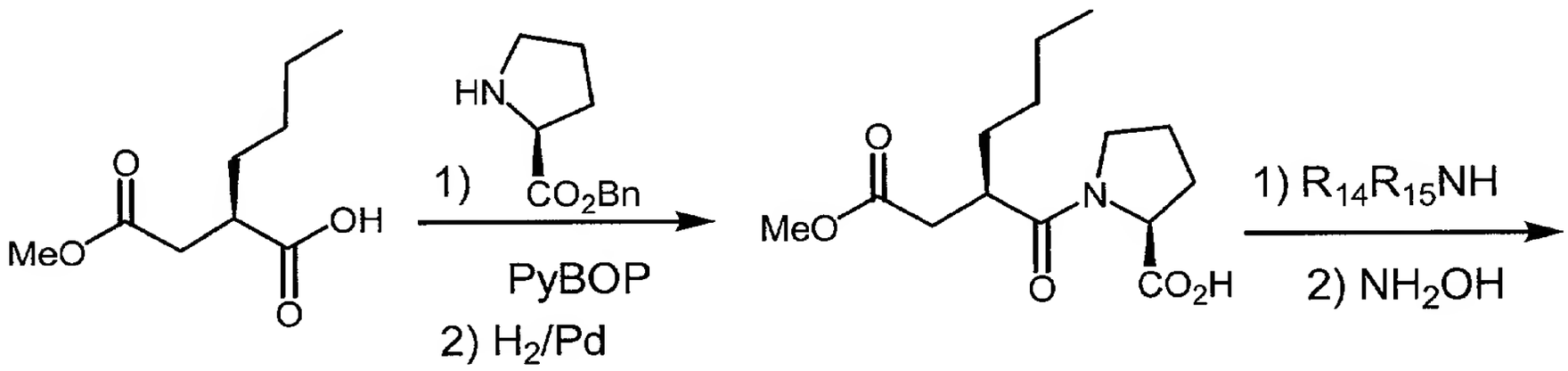
To resin **D-1** in DMF was added PFP-OTFA and pyridine and the mixture was shaken for 4 h. The resin was filtered and washed with DMF (3x), MeOH (2x), DCM (2x), and ether (2x) and dried under vacuum. To a portion of the resin was added a solution of an amine (1 mmol) and DIEA (1.5 mmol) in DMF (1 mL). The resin was shaken overnight, filtered and washed with DMF, MeOH, and DCM to afford **D-2**.

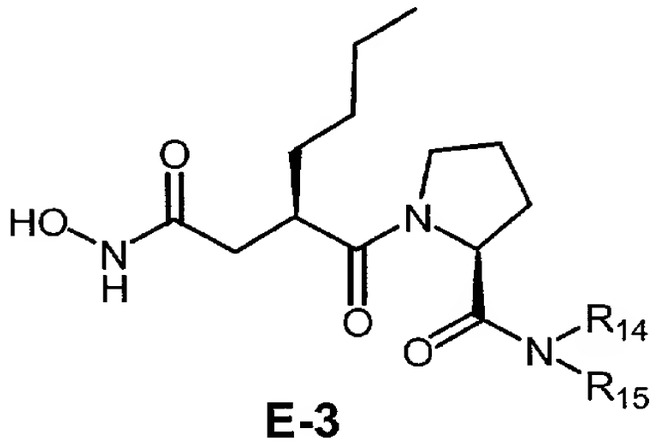
Step 3

To **D-2** was added dioxane (0.5 mL) and aqueous 50% hydroxylamine (1 mL). After 18 h, the cleavage products were drained and then purified by preparative reverse-phase (C18) HPLC to afford the desired hydroxamate **D-3**.

GENERAL PROCEDURE E

Synthesis of N-hydroxy-3-(*R*)-*n*-butyl-3-[2-(*S*)-aminocarbonylpyrrolidin-1-yl-carbonyl)propionamide





Step 1

To a solution of *mono*-4-methyl 2-(*R*)-butylsuccinic acid, (prepared in three steps from hexanoylchloride and t-butyl bromoacetate as described below; 1 mmol) in DMF was added proline O-benzyl ester (1 mmol), DIEA (0.4 mL, 2.3 mmol), and a coupling reagent (e.g. EDCI, PyBOP, DIC, etc.; 1 mmol). The mixture was stirred overnight, then diluted with ethyl acetate and washed with aqueous HCl (1 N), water, saturated sodium bicarbonate, brine, and then dried (Na_2SO_4). The filtrate was concentrated and then purified on silica gel (Merck 60; ethyl acetate/hexane) to afford methyl-3-(*R*)-butyl-3-(2-(*S*)-benzyloxycarbonylpyrrolidin-1-ylcarbonyl)propionate. To this amide (0.1 mmol) in ethylacetate (10 mL) was added 10 % Pd/C (100 mg) and the solution stirred under a hydrogen atmosphere for 8 h. The suspension was filtered through a Celite plug and then concentrated to afford methyl-3-(*R*)-butyl-3-(2-(*S*)-carboxypyrrolidin-1-ylcarbonyl)propionate **E-2**.

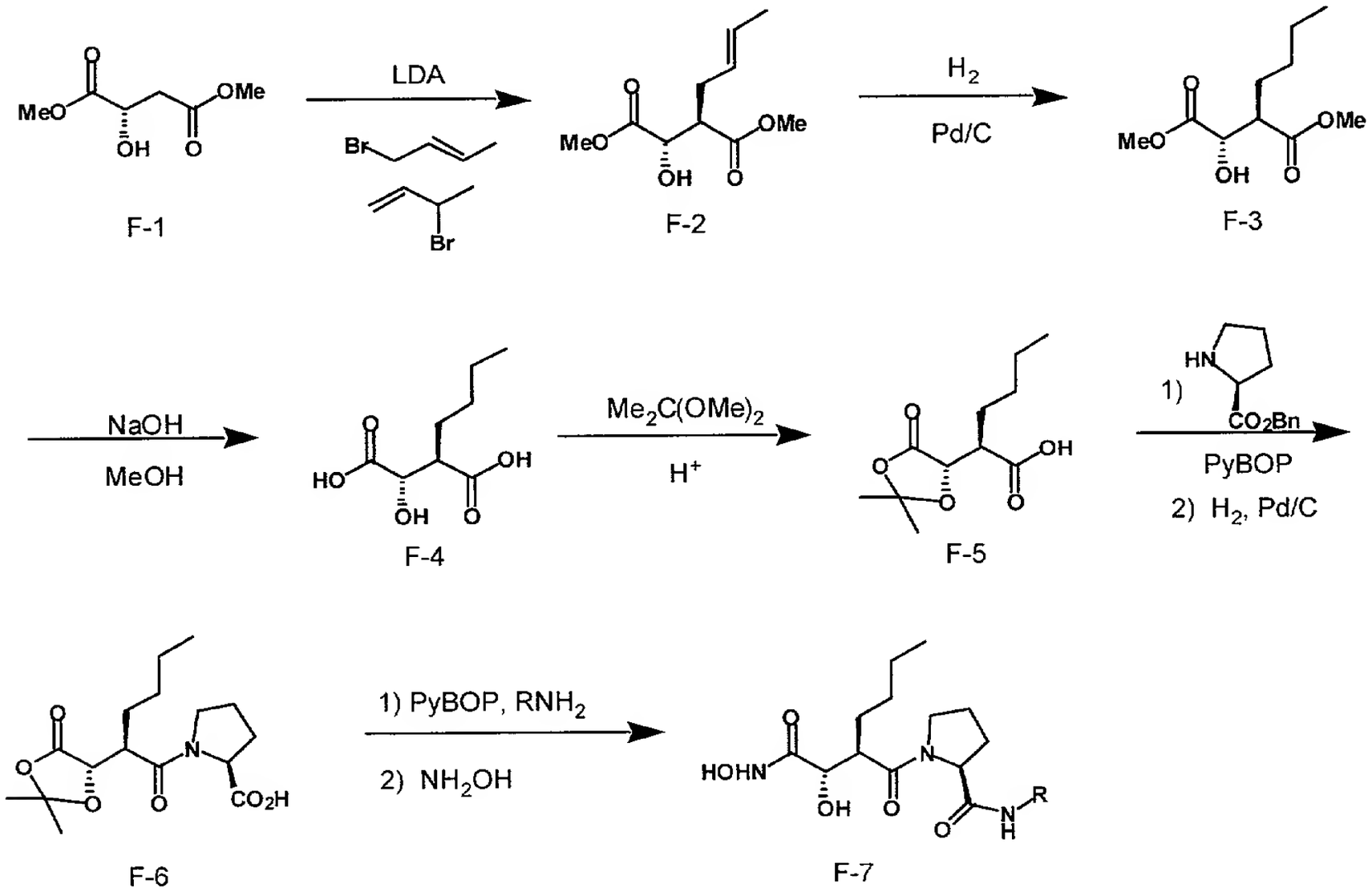
Step 2

To methyl-3-(*R*)-butyl-3-(2-(*S*)-carboxycarbonylpyrrolidin-1-ylcarbonyl)-propionate **E-2** (100 mg) in DMF (1 mL) was added an amine (1 equivalent), DIEA (2.5 equivalents) and HATU (1 equivalent) and the reaction stirred for 4 h. The

solution was then cooled to 0 °C, 50 % aqueous hydroxylamine was added (400 μL), and the reaction stirred at 4 °C for 4 hours to 3 days, depending upon the succinate. The crude reaction mixture was then purified by preparative reverse-phase (C18) HPLC to afford the desired compound methyl-3-(*R*)-butyl-3-(2-(*S*)-amino-carbonylpyrrolidin-1-ylcarbonyl)propionate **E-3**.

GENERAL PROCEDURE F

Synthesis of N-hydroxy-3-(*R*)-*n*-butyl-3-[2-(*S*)-aminocarbonylpyrrolidin-1-yl-carbonyl)-2-(*S*)-hydroxypropionamide



Step 1

To a solution of diisopropylamine (14 mL, 100 mmol) in THF at 0°C was added *n*-butyllithium (2.5 M in hexane, 40 mL, 100 mmol) over 10 min. The mixture was stirred at RT for 30 min., and then added *via* cannula to a -78 °C solution of dimethyl malate **F-1** (7.71 g, 47.6 mmol) in THF (130 mL). The mixture was warmed to -20 °C over 2 h, and then cooled to -78 °C. Crotyl bromide (8.1 g, 60 mmol) was added, then the mixture was allowed to warm to room temperature and then stirred overnight. The solution was then cooled to -10 °C and quenched with NH_4Cl (10%, 100 mL). The THF was removed and the residue extracted with ethyl acetate (2x200 mL). The combined organic layers were washed with HCl (1N, 3x50 mL), saturated

aqueous sodium bicarbonate (3x50 mL), and brine, then dried over Na_2SO_4. The solution was filtered and concentrated to give a residue, which was purified on silica gel (ethyl acetate/hexane 1:4) to afford (*2S,3R*)-3-(2-butenyl)-2-hydroxysuccinic dimethyl ester **F-2** (2.5 g, 24%).

Step 2

To (*2S,3R*)-3-(2-butenyl)-2-hydroxysuccinic dimethyl ester **F-2** (2.5 g) in ethyl acetate (50 mL) was added 10 % Pd/C (0.25g) and the reaction stirred under a hydrogen atmosphere for 20 h. The suspension was filtered through a pad of Celite, washed with EtOAc (3x) and then concentrated *in vacuo* to afford (*2S,3R*)-3-(*n*-butyl)-2-hydroxysuccinic dimethyl ester **F-3**.

Step 3

To (*2S,3R*)-3-(*n*-butyl)-2-hydroxysuccinic dimethyl ester **F-3** in methanol (28 mL) was added a solution of NaOH (2.2 g, 55 mmol) in water (28 mL). After 24 h the MeOH was removed, the crude reaction was acidified with HCl (6N, 12 mL) to pH = 1, and then extracted with ethyl acetate (3 x 50mL). The combined organic layers were dried (Na_2SO_4) and concentrated to give (*2S,3R*)-3-(*n*-butyl)-2-hydroxysuccinic acid **F-4** (1.96 g, 90%).

Step 4

To a solution of (*2S, 3R*)-3-(*n*-butyl)-2-hydroxysuccinic acid **F-4** (300 mg, 1.58 mmol) in 2,2-dimethoxypropane (10 mL) was added p-toluenesulfonic acid (20 mg) and the reaction was stirred at room temperature for 16 h. The solution was diluted with dichloromethaneand washed with brine, dried (Na_2SO_4) and then purified by silica gel chromatography to afford 1.2 mmol 2-(2,2-dimethyl-4-oxo-1,3-dioxolan-5-yl)hexanoic acid **F-5** (78 %).

Step 5

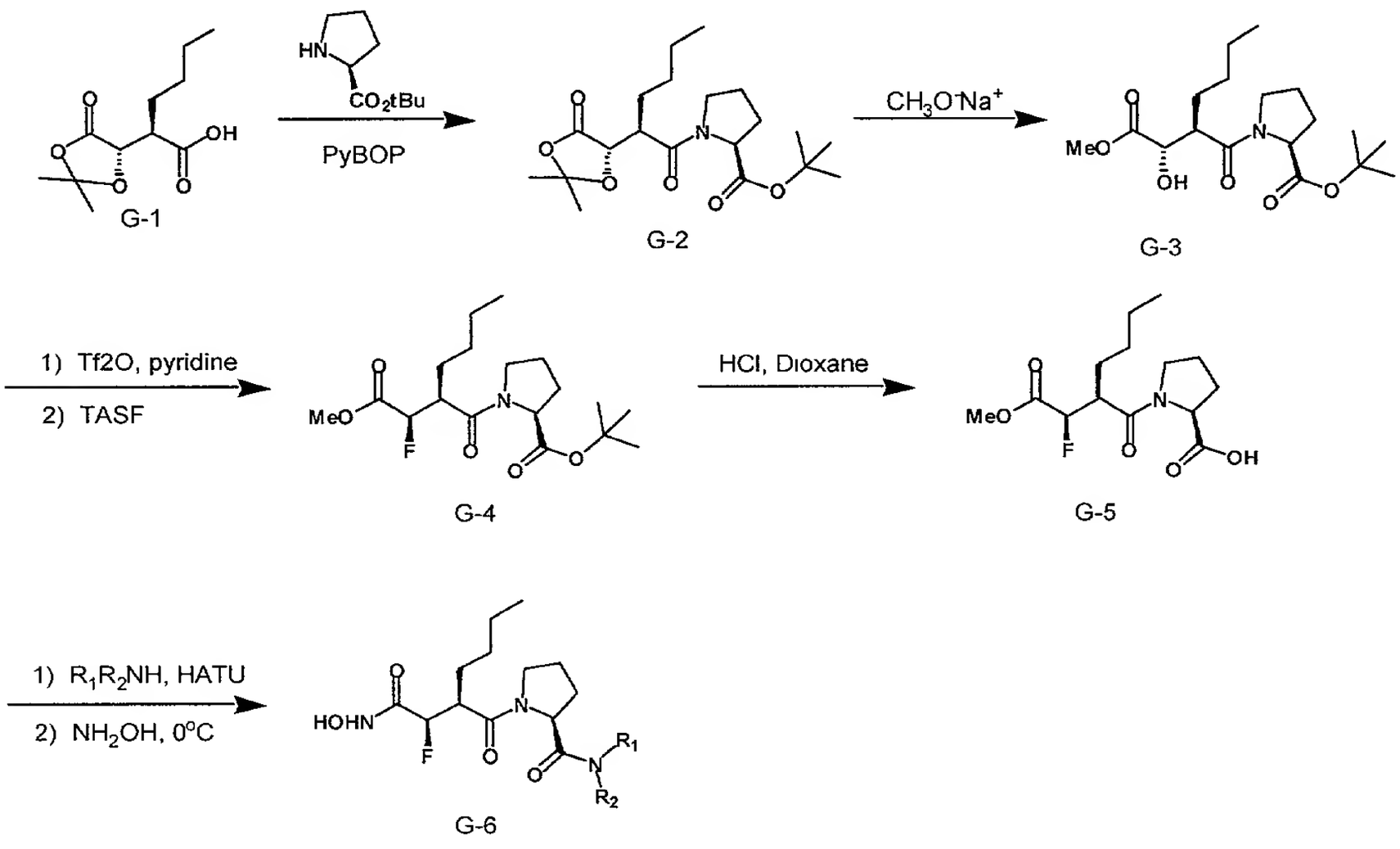
To a solution of 2-(2,2-dimethyl-4-oxo-1,3-dioxolan-5-yl)hexanoic acid **F-5** (1.2 mmol) in DCM (10 mL) was added L-Pro-OBn (1.2 mmol), PyBOP (1.2 mmol), and DIEA (2.5 mmol). The mixture was stirred overnight, then concentrated, and purified on silica gel (ethylacetate/hexane 1:4) to afford 275 mg of the desired amide (45%). To the product in ethylacetate (25 mL) was added 10 % Pd/C (50 mg) and the reaction stirred under a hydrogen atmosphere for 8 h. The suspension was filtered through a pad of Celite, washed with EtOAc (3x) and then concentrated *in vacuo* to afford 1-(2,2-dimethyl-4-oxo-1,3-dioxolan-5-yl)-1-(2-(*S*)-carboxy-pyrrolidin-1-ylcarbonyl)pentane **F-6** (quant.).

Step 6

To 1-(2,2-dimethyl- 4-oxo-1,3-dioxolan-5-yl)-1-(2-(*S*)-carboxy-pyrrolidin-1-ylcarbonyl)pentane **F-6** (50 mg) in dioxane (1 mL) was added an amine RNH_2 (1 equivalent), DIEA (2.5 equivalents) and HATU or PyBOP (1 equivalent) and the solution stirred for 4 h. The reaction was then cooled to 0 °C, 50 % aqueous hydroxylamine was added (400 μL), and the solution stirred at 4 °C for 8 hours. The crude reaction mixture was then purified by preparative reverse-phase (C18) HPLC to afford N-hydroxy-3-(*R*)-*n*-butyl-3-[2-(*S*)-aminocarbonylpyrrolidin-1-yl-carbonyl)-2-(*S*)-hydroxypropionamide **F-7**.

GENERAL PROCEDURE G

Synthesis of N-hydroxy-3-(*S*)-*n*-butyl-3-[2-(*S*)-aminocarbonylpyrrolidin-1-yl-carbonyl)-2-(*R*)-fluoropropionamide



Step 1

To 2-(2,2-dimethyl-4-oxo-1,3-dioxolan-5-yl)hexanoic acid **G-1** (10 mmol; prepared as described in Method F, above) in DMF (50 mL) was added proline O-t-butyl ester (10 mmol), DIEA (25 mmol) and PyBOP (10 mmol) and the solution stirred for 8 h. The reaction was diluted with ethyl acetate and washed with water, sodium bicarbonate, brine, and then dried (Na_2SO_4). The filtrate was concentrated and then purified on silica gel (Merck 60; ethyl acetate/hexane) to afford 1-(2 ,2-

dimethyl-4-oxo-1,3-dioxolan-5-yl)-1-(2-(*S*)-*tert*-butoxycarbonylpyrrolidin-1-yl-carbonyl)pentane **G-2** (5 mmol, 50 %).

Step 2

To 1-(2,2-dimethyl-4-oxo-1,3-dioxolan-5-yl)-1-(2-(*S*)-*tert*-butoxy-carbonylpyrrolidin-1-ylcarbonyl)pentane **G-2** (5 mmol, 50 %) (5 mmol) in methanol (20 mL) was added sodium methoxide (catalytic; pH adjusted to 10) and the solution stirred for 1 hour. Amberlite IR-120 resin (H^+ form) was added, then the solution was filtered and concentrated to afford methyl 3-(*R*)-*n*-butyl-3-[2-(*S*)-*tert*-butoxy-carbonylpyrrolidin-1-yl-carbonyl)-2-(*S*)-hydroxypropionate **G-3** (quant.).

Step 3

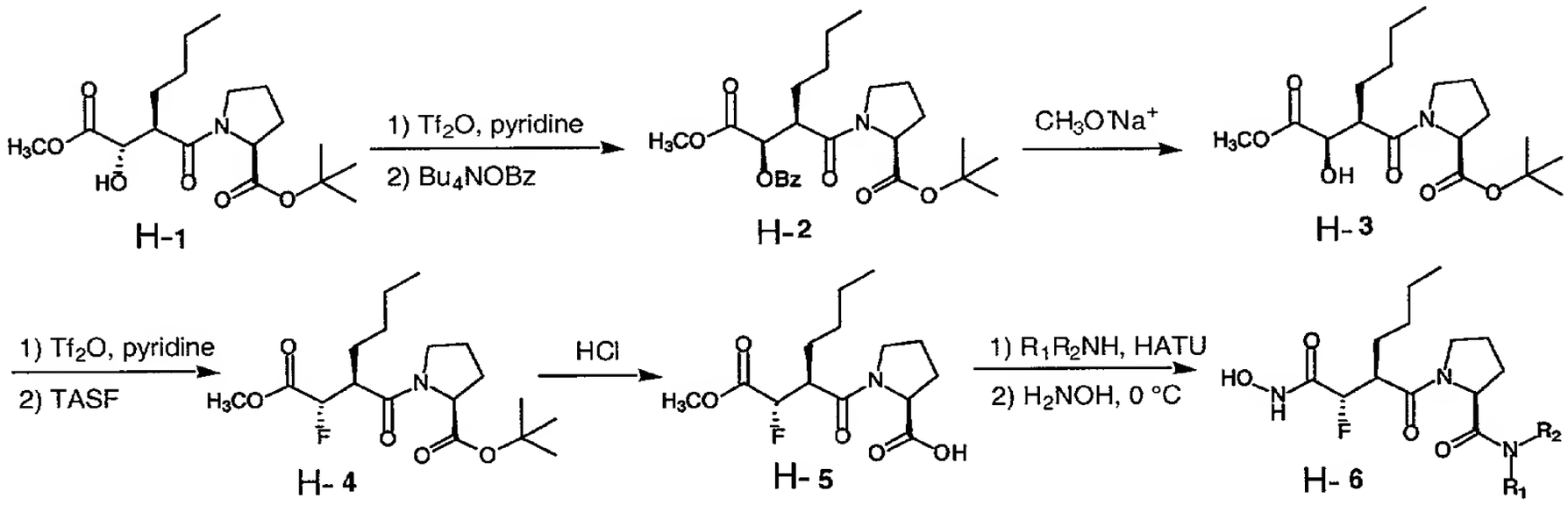
To methyl 3-(*R*)-*n*-butyl-3-[2-(*S*)-*tert*-butoxycarbonylpyrrolidin-1-yl-carbonyl)-2-(*S*)-hydroxypropionate **G-3** (5 mmol) in DCM (5 mL) was added pyridine (15 mmol), the reaction was cooled to –20 °C, then triflic anhydride was added (7.5 mmol). The solution was stirred for 1 hour, then washed with aqueous citric acid, sodium bicarbonate and brine, then dried (Na_2SO_4) and concentrated. The intermediate triflate was then resuspended in DCM and cooled to – 50 °C. Tris(dimethylamino)sulfur (trimethylsilyl)difluoride (TAS-F) was added (5 mmol) and the solution allowed to warm to rt. The reaction mixture was washed with aqueous sodium bicarbonate and brine, dried (Na_2SO_4) and concentrated then purified on silica gel (ethylacetate/hexanes) to afford 2.3 mmol (45 %) of methyl 3-(*S*)-*n*-butyl-3-[2-(*S*)-*tert*-butoxycarbonylpyrrolidin-1-yl-carbonyl)-2-(*R*)-fluoropropionate **G-4**.

Step 4

To methyl 3-(*S*)-*n*-butyl-3-[2-(*S*)-*tert*-butoxycarbonylpyrrolidin-1-yl-carbonyl)-2-(*R*)-fluoropropionate **G-4** (2.3 mmol) was added 4 N HCl in dioxane (10 mL), the solution stirred for 2 h, then evaporated to dryness to afford 2.3 mmol of methyl 3-(*S*)-*n*-butyl-3-[2-(*S*)-carboxypyrrolidin-1-yl-carbonyl)-2-(*R*)-fluoropropionate **G-5** (quant.). To intermediate **G-5** (0.15 mmol) in dioxane (1 mL) was added an amine (0.15 mmol), DIEA (0.38 mmol), and HATU or other coupling reagent (0.15 mmol) and the solution stirred for 8 h. The reaction was cooled to 0 °C, aqueous 50 % hydroxylamine was added (0.5 mL) and the reaction stirred for 4 h. The crude reaction mixture was then purified by preparative reverse-phase (C18) HPLC to afford N-hydroxy- 3-(*S*)-*n*-butyl-3-[2-(*S*)-aminocarbonylpyrrolidin-1-yl-carbonyl)-2-(*R*)-fluoropropionamide **G-6**.

GENERAL PROCEDURE H

Synthesis of N-hydroxy-3-(*S*)-*n*-butyl-3-[2-(*S*)-aminocarbonylpyrrolidin-1-yl-carbonyl)-2-(*S*)-fluoropropionamide



Step 1

To methyl 3-(*R*)-*n*-butyl-3-[2-(*S*)-*tert*-butoxycarbonylpyrrolidin-1-yl-carbonyl)-2-(*S*)-hydroxypropionate **H-1** (10 mmol; prepared as described in Method G, above) in DCM (10 mL) was added pyridine (30 mmol), the reaction was cooled to –20 °C then triflic anhydride (15 mmol) was added. The solution was stirred for 1 hour, then washed with aqueous citric acid, sodium bicarbonate and brine, then dried (Na_2SO_4) and concentrated. The resulting oil was dissolved in toluene (30 mL), cooled to 0 °C, then treated with tetrabutylammonium benzoate. After 1.5 h, the reaction was concentrated and then purified on silica gel (ethylacetate/hexanes) to afford 8.7 mmol of methyl 3-(*R*)-*n*-butyl-3-[2-(*S*)-*tert*-butoxycarbonylpyrrolidin-1-yl-carbonyl)-2-(*R*)-benzoyloxypropionate **H-2** (87 %).

Step 2

To methyl 3-(*R*)-*n*-butyl-3-[2-(*S*)-*tert*-butoxycarbonylpyrrolidin-1-yl-carbonyl)-2-(*R*)-benzoyloxypropionate **H-2** (8.7 mmol) in methanol (25 mL) at 0 °C was added sodium methoxide (catalytic; pH adjusted to 10) and the solution stirred for 2 h. Amberlite IR-120 resin (H^+ form) was added, then the solution was filtered and concentrated to afford methyl 3-(*R*)-*n*-butyl-3-[2-(*S*)-*tert*-butoxycarbonyl-pyrrolidin-1-yl-carbonyl)-2-(*R*)-hydroxypropionate **H-3** (quant.).

Step 3

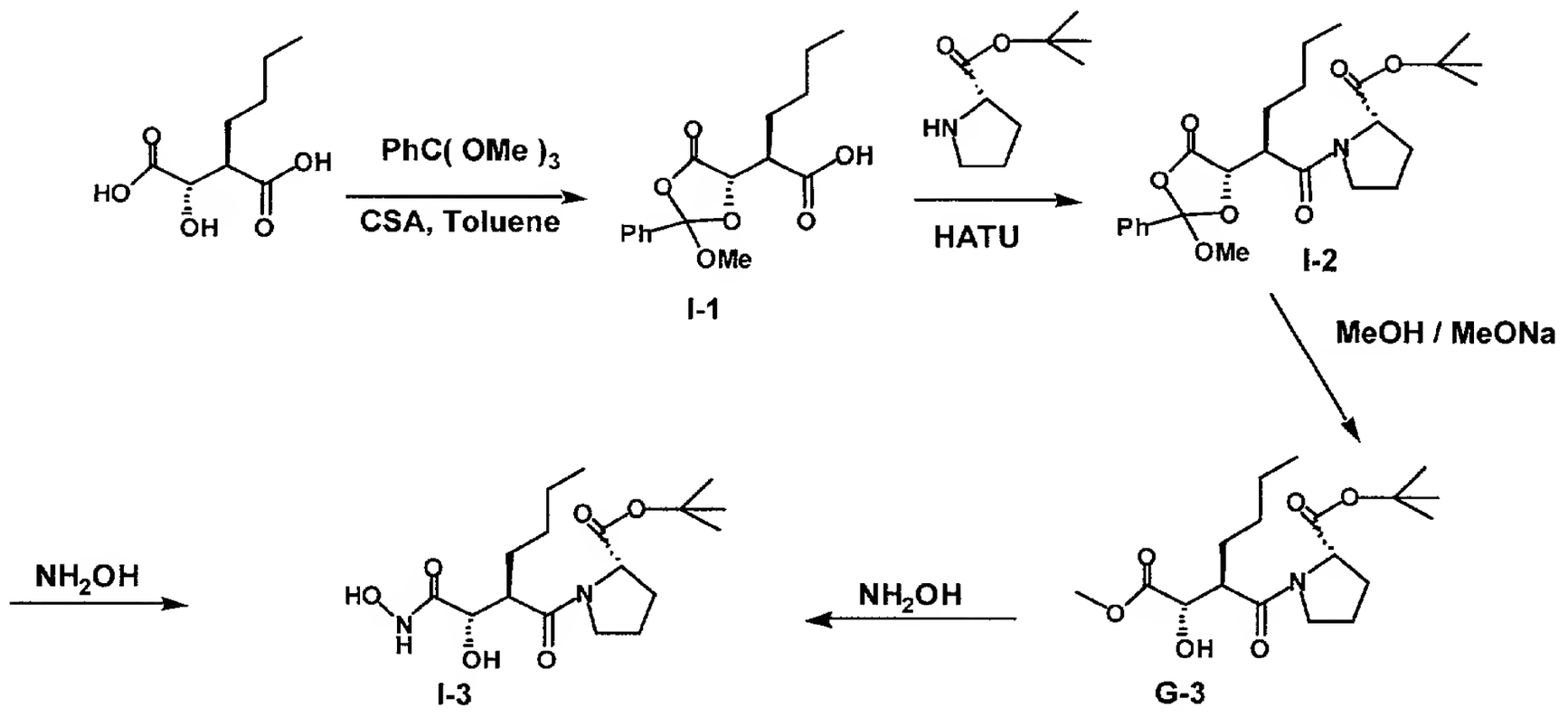
To methyl 3-(*R*)-*n*-butyl-3-[2-(*S*)-*tert*-butoxycarbonylpyrrolidin-1-yl-carbonyl)-2-(*R*)-hydroxypropionate **H-3** (8.7 mmol) in DCM (10 mL) was added pyridine (25 mmol), the reaction was cooled to –20 °C, then triflic anhydride (12.5 mmol) was added. The solution was stirred for 1 hour, then worked up as described above. The intermediate triflate was resuspended in DCM and cooled to –50 °C. Tris(dimethylamino)sulfur (trimethylsilyl)difluoride (TAS-F) was added (8.7 mmol) and the solution allowed to warm to rt. The reaction mixture was washed with aqueous sodium bicarbonate and brine, dried (Na_2SO_4) and concentrated, then purified on silica gel (ethylacetate/hexanes) to afford 4.3 mmol (50 %) of methyl 3-(*S*)-*n*-butyl-3-[2-(*S*)-*tert*-butoxycarbonylpyrrolidin-1-yl-carbonyl)-2-(*S*)-fluoropropionate **H-4**.

Step 4

To methyl 3-(*S*)-*n*-butyl-3-[2-(*S*)-*tert*-butoxycarbonylpyrrolidin-1-yl-carbonyl)-2-(*S*)-fluoropropionate **H-4** (4.3 mmol) was added 4 N HCl in dioxane (15 mL), the solution stirred for 2 h, then evaporated to dryness to afford 4.3 mmol of methyl 3-(*S*)-*n*-butyl-3-[2-(*S*)-carboxypyrrolidin-1-yl-carbonyl)-2-(*S*)-fluoro-propionate **H-5** (quant.). To **H-5** (0.15 mmol) in dioxane (1 mL) was added an amine (0.15 mmol), DIEA (0.38 mmol), and HATU or similar coupling reagent (0.15 mmol) and the solution stirred for 8 h. The reaction was cooled to 0 °C, aqueous 50 % hydroxylamine was added (0.5 mL) and the reaction stirred for 4 h. The crude reaction mixture was then purified by preparative reverse-phase (C18) HPLC to afford *N*-hydroxy-3-(*S*)-*n*-butyl-3-[2-(*S*)-aminocarbonylpyrrolidin-1-yl-carbonyl)-2-(*S*)-fluoropropionamide **H-6**.

GENERAL PROCEDURE I

Synthesis of N-hydroxy-3-(*R*)-*n*-butyl-3-[2-(*S*)-(tert-butoxycarbonyl)-pyrrolidin-1-yl-carbonyl)-2-(*S*)-hydroxypropionamide



Step 1

To a solution of (*2S,3R*)-3-(*n*-butyl)-2-hydroxysuccinic acid **F-4** (300 mg, 1.58 mmol) and powdered molecular sieves (1g) in trimethyl orthobenzoate (5 mL) and toluene (5ml) was added 10-Camphorsulfonic acid (20 mg) and the reaction was heated at 110°C under vacuum (20 torr) for 5 h. The solution was diluted with ethyl acetate , filtered through Celite and washed with brine, dried (Na_2SO_4) and then purified by silica gel chromatography to afford 1.2 mmol 2-(2-methoxy-2-phenyl -4-oxo-1,3-dioxolan-5-yl)hexanoic acid **I-1** (40 %).

Step 2

To 2-(2-methoxy-2-phenyl -4-oxo-1,3-dioxolan-5-yl)hexanoic acid **I-1** (10 mmol; prepared as described in Method I, above) in DMF (50 mL) was added proline O-t-butyl ester (10 mmol), DIEA (25 mmol) and PyBOP (10 mmol) and the solution stirred for 8 h. The reaction was diluted with ethyl acetate and washed with water, sodium bicarbonate, brine, and then dried (Na_2SO_4). The filtrate was concentrated and then purified on silica gel (Merck 60; ethyl acetate/hexane) to afford 1-(2 – methoxy-2-phenyl -4-oxo-1,3-dioxolan-5-yl)-1-(2-(*S*)-*tert*-butoxycarbonylpyrrolidin-1-yl-carbonyl)pentane **I-2** (5 mmol, 50 %).

Step 3

To 1-(2-methoxy-2-phenyl-4-oxo-1,3-dioxolan-5-yl)-1-(2-(*S*)-*tert*-butoxy-carbonylpyrrolidin-1-ylcarbonyl)pentane **I-2** (5 mmol, 50 %) (5 mmol) in methanol (20 mL) was added sodium methoxide (catalytic; pH adjusted to 10) and the solution stirred for 1 hour. Amberlite IR-120 resin (H^+ form) was added, then the solution was

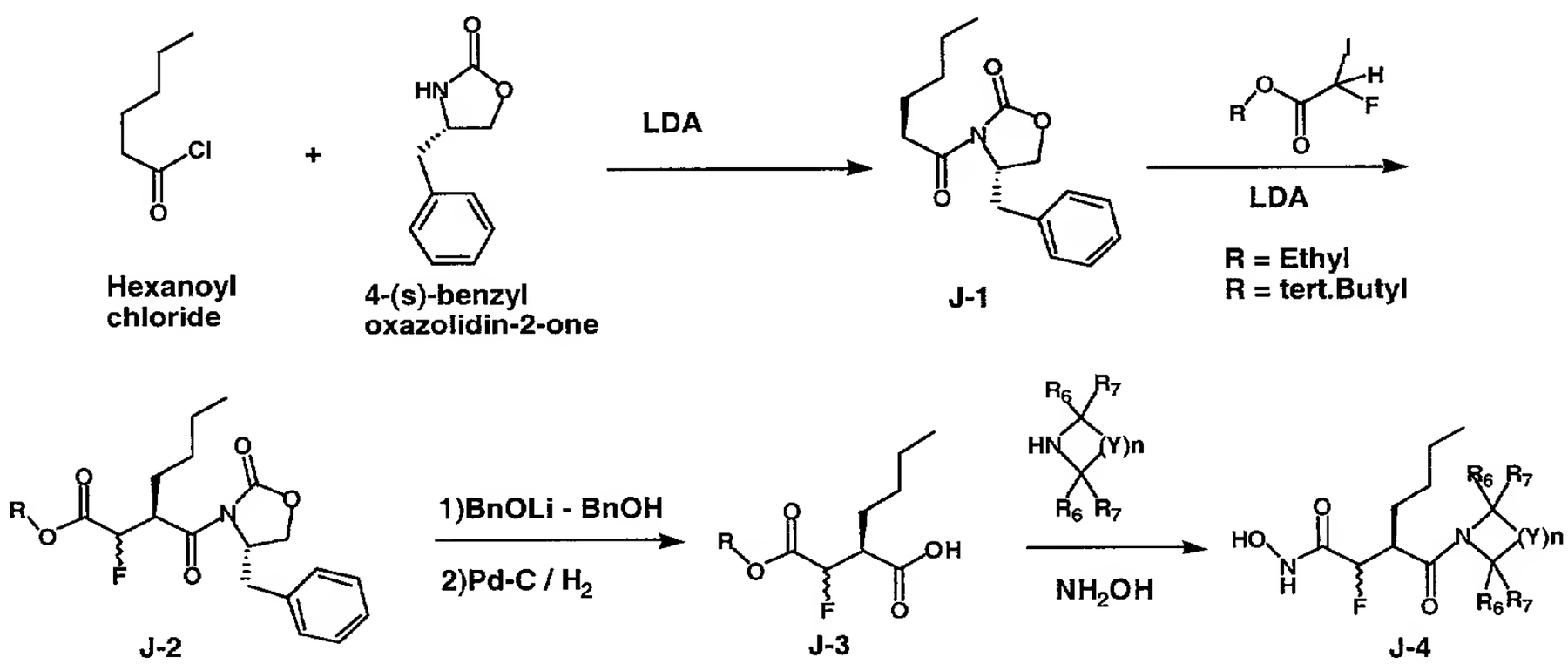
filtered and concentrated to afford methyl 3-(*R*)-*n*-butyl-3-[2-(*S*)-*tert*-butoxy-carbonylpyrrolidin-1-yl-carbonyl)-2-(*S*)-hydroxypropionate **G-3** (quant.).

Step 4

To **G-3** and **I-2** (50mg) in dioxane (1 mL) was added aqueous 50 % hydroxylamine (0.5 mL) and the reaction stirred for 16 h. The crude reaction mixture was then purified by preparative reverse-phase (C18) HPLC to afford N-hydroxy-3-(*R*)-*n*-butyl-3-[2-(*S*)-(*tert*-butoxycarbonyl)-pyrrolidin-1-yl-carbonyl)-2-(*S*)-hydroxypropionamide.

GENERAL PROCEDURE J

Synthesis of N-hydroxy-3-(*S*)-*n*-butyl-3-[2-(*S*)-aminocarbonylpyrrolidin-1-yl-carbonyl)-2-(*RS*)-fluoropropionamide



Step 1

To a solution of 4-(*S*)-benzyloxazolidin-2-one (56 mmol) (Aldrich, Milwaukee, Wisconsin) in THF at –78 °C was added 2.5 M *n*-BuLi in hexane (22.4 mL, 56 mmol) and the reaction stirred at –78 °C for 2 hr. To this was added via cannula a –78 °C solution of hexanoyl chloride (65 mmol) in THF and the mixture stirred at –78 °C for 2 hr, then allowed to warm to room temperature and stirred overnight. The reaction was then quenched with aqueous saturated NH_4Cl, extracted with ethyl acetate, dried, and purified by silica gel chromatography (hexanes/ethyl acetate) to afford *N*-hexanoyl-4-(*S*)-benzyloxazolidin-2-one **J-1**.

Step 2

To a solution of *N*-hexanoyl-4-(*S*)-benzyloxazolidin-2-one (7.3 mmol) in THF at –78 °C was added 1.0 M sodium hexamethyldisilazide (NaHMDS, 8.8 mmol) and the reaction stirred at –78 °C for 1 hr. A solution of alkyl iodofluorooacetate (8.8 mmol) in THF was then added dropwise, and the resulting mixture was stirred at –78 °C for 1 hr and then at room temperature overnight. The reaction was quenched with NH_4Cl, concentrated, then suspended in ethyl acetate and washed with 0.5 N HCl and brine, dried, and purified by silica gel chromatography (ethyl acetate/hexanes) to afford the alkyl 3-(*S*)-(*n*-butyl)-3-[4-(*S*)-benzyloxazolidin-2-one-3-ylcarbonyl)-2-(*RS*)-(fluoro)propionate **J-2**.

Step 3

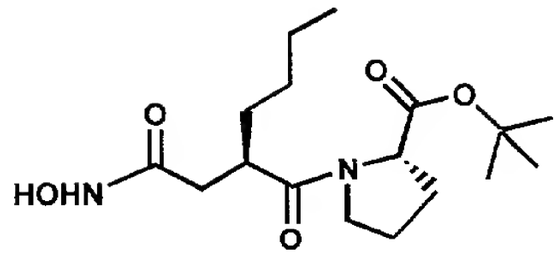
To alkyl 3-(*S*)-(*n*-butyl)-3-[4-(*S*)-benzyloxazolidin-2-one-3-ylcarbonyl)-2-(*RS*)-(fluoro)propionate (1.44 mmol) in THF at 0°C was added LiOBn (5.76 mmol) in benzyl aicohol and the reaction stirred at 0°C for 3 hr. The reaction was then quenched with 5% $KHSO_4$, concentrated, suspended in ethyl acetate and subjected to standard aqueous workup. The crude product was purified by silica gel chromatography (methanol/dichloromethane) to afford alkyl 3-(*R*)-(*n*-butyl)-2-(*RS*)-(fluoro)propionate **J-3**.

Step 4

To **J-3** (0.15 mmol) in dioxane (1 mL) was added an amine (0.15 mmol), DIEA (0.38 mmol), and HATU or similar coupling reagent (0.15 mmol) and the solution stirred for 8 h. The reaction was cooled to 0 °C, aqueous 50 % hydroxylamine was added (0.5 mL) and the reaction stirred for 4 h. The crude reaction mixture was then purified by preparative reverse-phase (C18) HPLC to afford *N*-hydroxy-3-(*S*)-*n*-butyl-3-[2-(*S*)-aminocarbonylpyrrlidin-1-yl-carbonyl)-2-(*RS*)-fluoropropionamide **J-4**.

Example 1

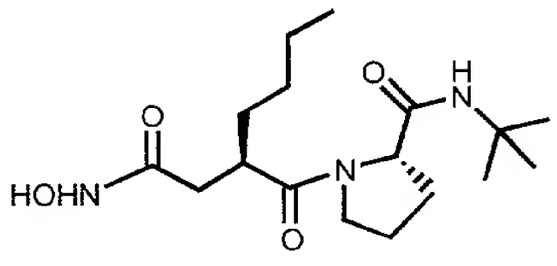
Synthesis of *N*-hydroxy-3-(*R*)-(*n*-butyl)-3-[(2-(*S*)-(*tert*-butoxycarbonyl)-pyrrolidin-1-ylcarbonyl]propionamide



The title compound was prepared according to General Procedure A from *mono*-methyl 2-(*R*)-butylsuccinic acid and L-proline *tert*-butyl ester. This compound has also been prepared according to General Procedure D using L-proline *tert*-butyl ester as the amine. ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.89 (t, J=7.2 Hz, 3 H), 1.43 (s, 9H), 1.24-1.71 (m, 6H), 1.86-2.43 (m, 5H), 2.53 (dd, J=10.5 and 13.2 Hz, 1 H), 3.06 (m, 1H), 3.45-3.80 (m, 2H), 4.28-4.40 (m, 1H).

Example 2

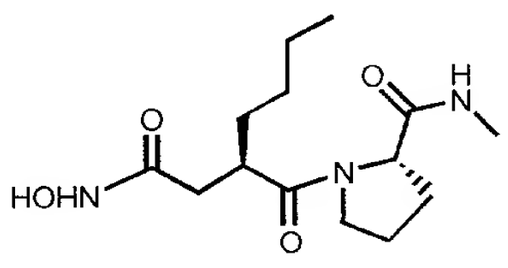
Synthesis of *N*-hydroxy-3-(*R*)-(*n*-butyl)-3-[(2-(*S*)-(*tert*-butylaminocarbonyl)-pyrrolidin-1-ylcarbonyl]propionamide



The title compound was prepared according to General Procedure A from *mono*-methyl 2-(*R*)-butylsuccinic acid and L-proline t-butylamide hydrochloride. ^{1}H NMR (300 MHz, $CDCl_3$) : δ 0.77 (t, J=7.2 Hz, 3H), 1.19 (s, 9H), 1.28-2.00 (m, 10H), 2.08 (dd, J= 4.1 and 9.6 Hz, 1H), 2.26 (dd, J =9.6 and 15 Hz, 1H), 2.99 (m, 1H), 3.47 (m, 1H), 3.63 (dd, J=9.0 and 16.8 Hz, 1H), 4.28 (dd, J=1.9 and 7.8 Hz, 1H).

Example 3

Synthesis of *N*-hydroxy-3-(*R*)-(*n*-butyl)-3-[(2-(*S*)-(methylaminocarbonyl)-pyrrolidin-1-ylcarbonyl]propionamide



Small-scale synthesis

The title compound was prepared according to General Procedure A from *mono*-methyl 2-(*R*)-butylsuccinic acid and L-proline methylamide hydrochloride. ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.80 (t, J=7.2 Hz, 3H), 1.28-2.50 (m, 12H), 2.98 (m, 1H), 3.47 s, 3H), 3.58 (m, 2H), 4.27 (m, 1H).

Large-scale synthesis

Step 1

To a solution of Boc-Pro-OH (5 g, 23.2 mmol), methylamine (2M in THF, 15 mL, 30 mmol), EDC (4.79 g, 25 mmol), and HOBt (3.38 g, 25 mmol) in THF (150 mL) was added DIEA (4.35 mL, 25 mmol) and the mixture stirred overnight. THF was removed, the residue was dissolved in ethyl acetate and then washed with aqueous HCl (1 N, 2x), 5% KHSO4 (2x), saturated sodium bicarbonate, brine, dried (Na_2SO_4), concentrated, and purified on silica gel (Merck 60, ethyl acetate/hexanes) to give N-Boc-(2-methylaminocarbonyl)pyrrolidine (3.3 g, 63%).

Step 2

N-Boc-(2-methylaminocarbonyl)pyrrolidine (3.3 g, 14.5 mmol) was treated with HCl (4 N in dioxane, 10 mL) for 1 h. The solvent was removed and the white solid treated with *mono*-methyl 2-(*R*)-butylsuccinic acid (2.82 g, 15 mmol), HOBt (2.02 g, 15 mmol), EDC (2.88 g, 15 mmol) and DIEA (6.96 mL, 40 mmol) in THF for 16 h. Similar work-up and purification gave the methyl ester (2.2 g). A solution of methyl ester and lithium hydroxide (400 mg, 10 mmol) in methanol (15 mL) and water (10 mL) was stirred for 16 h. Methanol was removed and the aqueous layer was acidified to pH =1 and extracted with ethyl acetate (4x). The organic layers were dried (Na_2SO_4) and concentrated to afford 3-(*R*)-(*n*-butyl)-3-[(2-(*S*)-(methylamino-carbonyl)pyrrolidin-1-ylcarbonyl]propionic acid as a white solid (1.5 g).

Step 3

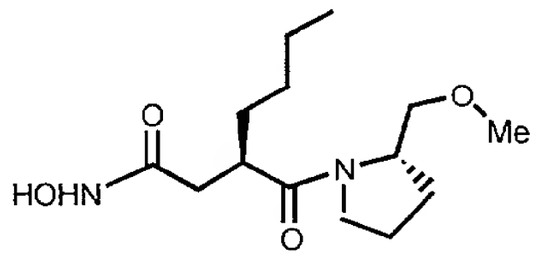
To a solution of 3-(*R*)-(*n*-butyl)-3-[(2-(*S*)-(methylaminocarbonyl)-pyrrolidin-1-ylcarbonyl]propionic acid (1.5 g, 5.28 mmol), O-benzylhydroxylamine (932 mg, 5.84 mmol), HOBt (784 mg, 5.84 mmol), and DIEA (2.3 mL, 13.2 mmol) in THF (100 mL) was added EDC (1.12 g, 5.84 mmol) and the reaction stirred for 16 h. Conventional work-up and purification gave *N*-benzyloxy-3-(*R*)-(*n*-butyl)-3-[(2-(*S*)-(methylaminocarbonyl)pyrrolidin-1-ylcarbonyl]propionamide (1.56 g).

A solution of *N*-benzyloxy-3-(*R*)-(*n*-butyl)-3-[(2-(*S*)-(methylaminocarbonyl)-pyrrolidin-1-ylcarbonyl]propionamide (1.5 g) in ethyl acetate (50 mL) was

hydrogenated over Pd/C for 14 h. The mixture was filtered through a pad of Celite, washed with ethyl acetate, and concentrated to give *N*-hydroxy-3-(*R*)-(*n*-butyl)-3-[(2-(*S*)-(methylamino-carbonyl)pyrrolidin-1-ylcarbonyl]propionamide (1.1 g).

Example 4

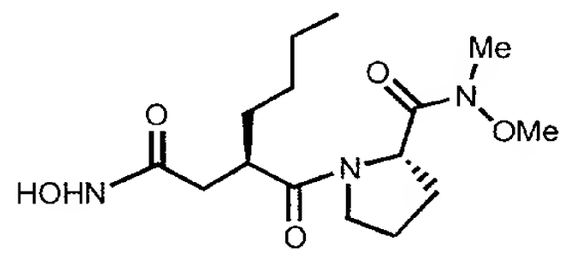
Synthesis of *N*-hydroxy-3-(*R*)-(*n*-butyl)-3-[(2-(*S*)-(methoxymethyl)-pyrrolidin-1-ylcarbonyl]propionamide



The title compound was prepared according to General Procedure A from (*S*)-(+)-2-(methoxymethyl)pyrrolidine and *mono*-methyl 2-(*R*)-butylsuccinic acid. ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.90 (t, J=7.5 Hz, 3H), 1.22-1.64 (m, 6H), 1.84-2.05 (m, 2H), 1.84-2.05 (m, 2H), 2.25-2.42 (m, 1H), 2.51-2.66 (m, 1H), 2.99-3.16 (m, 1H), 3.33 (s, 3H), 3.38 (dd, J=1.9 and 6.9 Hz, 1H), 3.44 (bd, J = 6.9 Hz, 1H), 3.47-3.54 (m, 1H), 3.61-3.69 (m, 1H), 4.24 (m, 1H).

Example 5

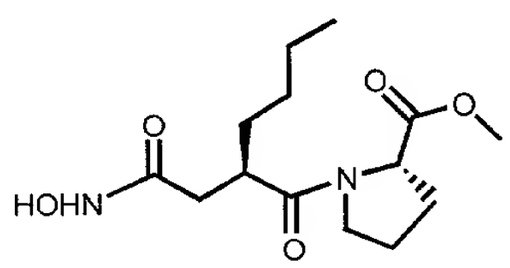
Synthesis of *N*-hydroxy-3-(*R*)-(*n*-butyl)-3-[(2-(*S*)-(*N*-methoxy-*N*-methylamino-carbonyl)pyrrolidin-1-ylcarbonyl]propionamide



The title compound was prepared according to General Procedure A from L-proline N-methoxyl N-methylamide hydrochloride and *mono*-methyl 2-(*R*)-butylsuccinic acid. ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.80 (t, J=7.2 Hz, 3H), 1.27-2.60 (m, 12H), 3.05 (m, 1H), 3.19 (s, 3H), 3.72 (m, 2H), 3.78 (s, 3H), 4.85 (m, 1H).

Example 6

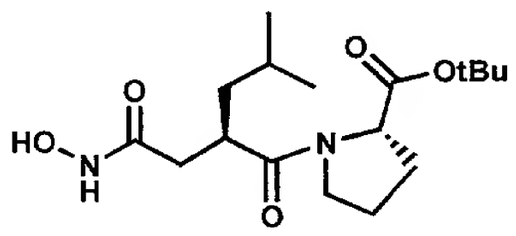
Synthesis of *N*-hydroxy-3-(*R*)-(*n*-butyl)-3-[(2-(*S*)-(methoxycarbonyl)-pyrrolidin-1-ylcarbonyl]propionamide



The title compound was prepared according to General Procedure A from L-proline methyl ester hydrochloride and *mono*-methyl 2-(*R*)-butylsuccinic acid. ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.90 (m, 3H), 1.23-1.70 (m, 6H), 1.86-2.09 (m, 3H), 2.15-2.62 (m, 3H), 3.01-3.17 (m, 1 H), 3.59 –3.86 (m, 2H), 3.71 (s, 3H), 4.42-4.53(m, 1H).

Example 7

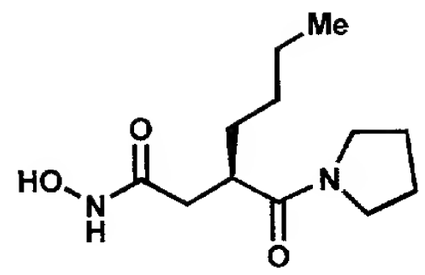
Synthesis of *N*-hydroxy-3-(*R*)-(3-methylpropyl)-3-[(2-(*S*)-(*tert*-butoxycarbonyl)-pyrrolidin-1-ylcarbonyl]propionamide



The title compound was prepared according to General Procedure A from L-proline *t*-butyl ester hydrochloride and *mono*-methyl 2-(*R*)-isobutylsuccinic acid. ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.90-0.99 (m, 6H), 1.27-2.58 (m, 18H), 2.78-2.91 (m, 1H), 3.08-3.18 (m, 1H), 3.43-3.81 (m, 3H), 4.26-4.40 (m, 2H).

Example 8

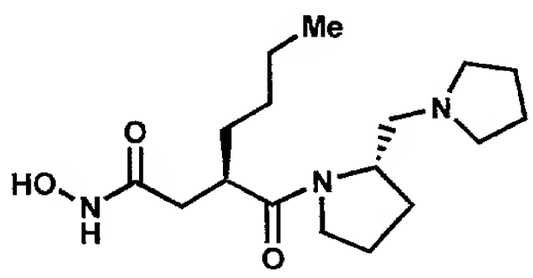
Synthesis of *N*-hydroxy-3-(*R*)-(*n*-butyl)-3-(pyrrolidin-1-ylcarbonyl)propionamide



The title compound was prepared according to General Procedure A using pyrrolidine as the amine and mono methyl-2-(*R*)-butylsuccinic acid. MS (APCI) m/z = 243 [M+H].

Example 9

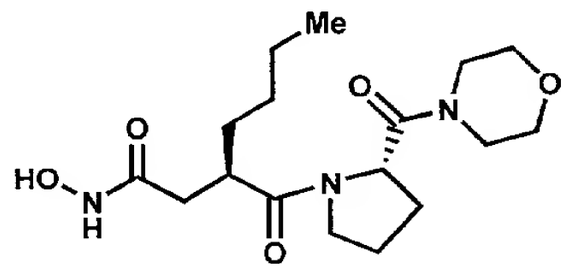
Synthesis of *N*-hydroxy-3-(*R*)-(*n*-butyl)-3-[(2-(*S*)-(pyrrolidin-1-ylmethyl)-pyrrolidin-1-ylcarbonyl]propionamide



The title compound was prepared according to General Procedure A from 2-(S)-(pyrrolidin-1-ylmethyl)pyrrolidine and *mono*-methyl 2-(*R*)-butylsuccinic acid. MS (APCI) m/z = 326 [M+H].

Example 10

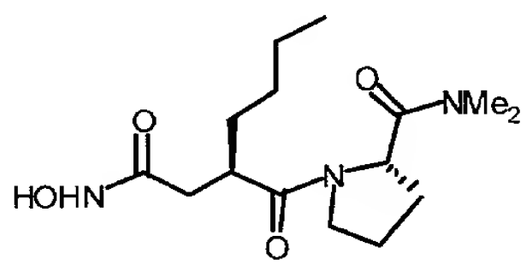
Synthesis of *N*-hydroxy-3-(*R*)-(*n*-butyl)-3-[(2-(*S*)-(morpholin-4-ylcarbonyl)-pyrrolidin-1-ylcarbonyl]propionamide



The title compound was prepared according to General Procedure D using L-proline N-morpholinylamide as the amine. MS (APCI) m/z = 356 [M+H].

Example 11

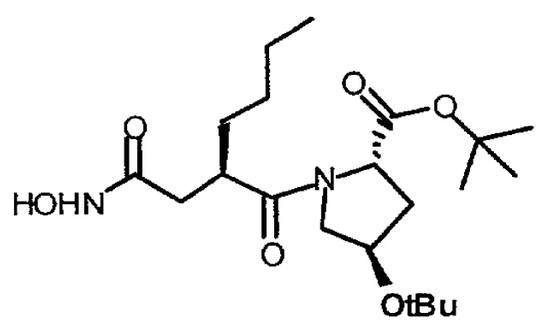
Synthesis of *N*-hydroxy-3-(*R*)-(*n*-butyl)-3-[(2-(*S*)-(dimethylaminocarbonyl)-pyrrolidin-1-ylcarbonyl]propionamide



The title compound was prepared according to General Procedure A from L-proline N,N-dimethylamide hydrochloride and *mono*-methyl 2-(*R*)-butylsuccinic acid. MS (APCI) m/z = 314 [M+H].

Example 12

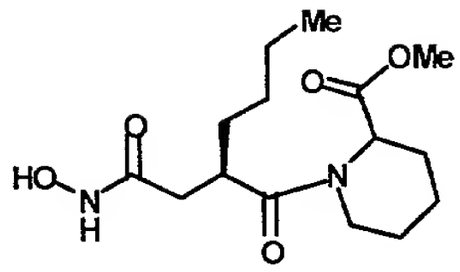
Synthesis of *N*-hydroxy-3-(*R*)-(*n*-butyl)-3-[4-(*R*)-(*tert*-butoxy-2-(*S*)-*tert*-butoxycarbonyl)pyrrolidin-1-ylcarbonyl]propionamide



The title compound was prepared according to General Procedure A from 3-(*R*)-O-*tert*-butyloxy-L-proline t-butyl ester and *mono*-methyl 2-(*R*)-butylsuccinic acid. MS (APCI) m/z = 415 [M+H].

Example 13

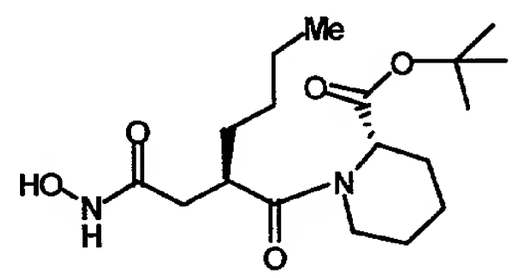
Synthesis of *N*-hydroxy-3-(*R*)-(*n*-butyl)-3-[2-(*S*)-(methoxycarbonyl)piperidin-1-ylcarbonyl]propionamide



The title compound was prepared according to General Procedure A from (±)-homoproline methyl ester and *mono*-methyl 2-(*R*)-butylsuccinic acid. MS (APCI) m/z = 315 [M+H].

Example 14

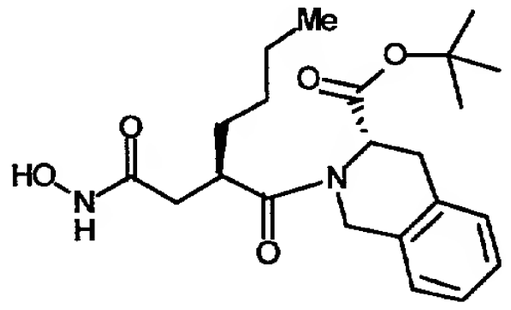
Synthesis of *N*-hydroxy-3-(*R*)-(*n*-butyl)-3-[2-(*S*)-(*tert*-butoxycarbonyl)piperidin-1-ylcarbonyl]propionamide



The title compound was prepared according to General Procedure D using L-homoproline t-butyl ester as the amine. MS (APCI) m/z = 357 [M+H].

Example 15

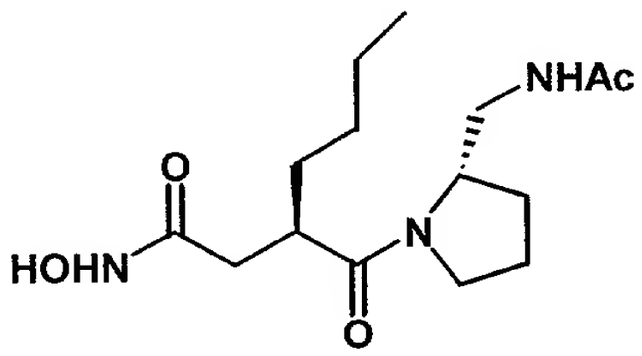
Synthesis of *N*-hydroxy-3-(*R*)-(*n*-butyl)-3-[2-(*S*)-(*tert*-butoxycarbonyl)-tetrahydroisoquinolin-1-ylcarbonyl]propionamide



The title compound was prepared according to General Procedure A from L-tetrahydroisoquinoline t-butyl ester and *mono*-methyl 2-(*R*)-butylsuccinic acid. MS (APCI) m/z = 405 [M+H].

Example 16

Synthesis of *N*-hydroxy-3-(*R*)-(*n*-butyl)-3-[2-(*S*)-(acetamidomethyl)pyrrolidin-1-ylcarbonyl]propionamide



Step 1

To a solution of 4-(*S*)-benzyloxazolidin-2-one (56 mmol) (Aldrich, Milwaukee, Wisconsin) in THF at –78 °C was added 2.5 M *n*-BuLi in hexane (22.4 mL, 56 mmol) and the reaction stirred at –78°C for 2 hr. To this was added via cannula a –78 °C solution of hexanoyl chloride (65 mmol) in THF and the mixture stirred at –78 °C for 2 hr, then allowed to warm to room temperature and stirred overnight. The reaction was then quenched with aqueous saturated NH_4Cl, extracted with ethyl acetate, dried, and purified by silica gel chromatography (hexanes/ethyl acetate) to afford *N*-hexanoyl-4-(*S*)-benzyloxazolidin-2-one.

Step 2

To a solution of *N*-hexanoyl-4-(*S*)-benzyloxazolidin-2-one (7.3 mmol) in THF at –78°C was added 1.0 M sodium hexamethyldisilazide (NaHMDS, 8.8 mmol) and the reaction stirred at –78°C for 1 hr. A solution of methyl bromoacetate (8.8 mmol) in THF was then added dropwise, and the resulting mixture was stirred at –78°C for 1 hr and then at room temperature overnight. The reaction was quenched with NH_4Cl, concentrated, then suspended in ethyl acetate and washed with 0.5 N HCl and brine, dried, and purified by silica gel chromatography (ethyl acetate/hexanes) to afford the methyl 3-(*R*)-(*n*-butyl)-3-[4-(*S*)-benzyloxazolidin-2-one-3-ylcarbonyl)propionate.

Step 3

To methyl 3-(*R*)-(*n*-butyl)-3-[4-(*S*)-benzyloxazolidin-2-one-3-ylcarbonyl)-propionate (1.44 mmol) in THF/water at 0°C was added 30% H_2O_2 (5.76 mmol) and solid lithium hydroxide (1.44 mmol) and the reaction stirred at 0°C for 3 hr. The reaction was then quenched with 2.0 M Na_2SO_3, concentrated, suspended in ethyl acetate and subjected to standard aqueous workup. The crude product was purified by

silica gel chromatography (methanol/dichloromethane) to afford methyl 3-(*R*)-(*n*-butyl)-propionate.

Step 4

To Boc-L-prolinol (1 mmol) (Advanced Chemtech, Louisville, KY) in THF at 0°C was added mesitylenesulfonylchloride (MsCl, 1.2 mmol) and DIEA (1.5 mmol) and the solution allowed to warm to rt, then stirred an additional hour. Solid sodium azide was added (1.5 mmol) and the reaction was allowed to stir overnight. Conventional aqueous workup followed by silica gel chromatography afforded the N-Boc-(*S*)-(2-azidomethyl)pyrrolidine.

Step 5

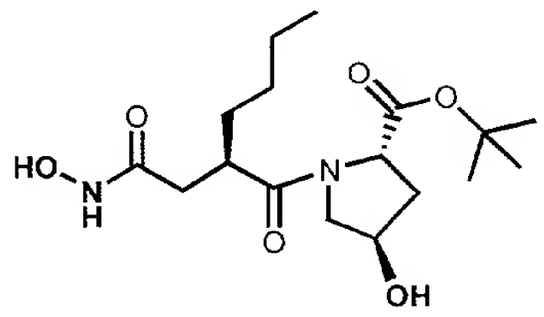
A solution of the N-Boc-(*S*)-(2-azidomethyl)pyrrolidine in ethylacetate was added to 10% Pd/C and the reaction evacuated and flushed with hydrogen gas three times. The reaction was then stirred under a hydrogen atmosphere overnight, then filtered through a pad of celite and concentrated to dryness. The resulting amine was dissolved in DMF and then acylated with acetic anhydride to afford the N-Boc-(*S*)-(2-acetamidomethyl)pyrrolidine. The Boc group was deprotected with 1N HCl in dioxane to afford the desired (*S*)-(2-acetamidomethyl)pyrrolidine.

Step 6

The title compound was prepared from (*S*)-(2-acetamidomethyl)pyrrolidine and methyl 3-(*R*)-(*n*-butyl)propionate according to General Procedure A.
MS (APCI) m/z = 314 [M+H].

Example 17

Synthesis of *N*-hydroxy-3-(*R*)-(*n*-butyl)-3-[(4-(*R*)-hydroxy-2-(*S*)-*tert*-butoxycarbonyl)pyrrolidin-1-ylcarbonyl]propionamide



Small-scale synthesis

Step 1

Cbz-protected *trans*-3-hydroxy-L-proline (20 g, 75 mmol) in DCM was treated with 60 ml of acetic anhydride and 10 mL of pyridine. The solution was stirred at rt for 18 hours, then the reaction was quenched with icewater, extracted with EtOAc (3 x 200 mL), and the organic layer washed with water, brine, and dried over $MgSO_4$. Concentration *in vacuo* gave Cbz-protected *trans*-3-acetoxy-L-proline as a colorless oil.

Step 2

To a solution of Cbz-protected *trans*-3-acetoxy-L-proline (75 mmol) in dry dioxane was added *tert*-butyl alcohol (14.2 mL, 150 mmol), diisopropylcarbodiimide (23 mL, 147 mmol), and DMAP (2.3 g) and the mixture was stirred at rt for two days. The reaction was concentrated to an oil and purified via silica gel chromatography (hexanes/ethyl acetate) to afford the desired Cbz-protected *trans*-3-acetoxy-L-proline t-butyl ester. ESMS (negative): 362 (M-1).

Step 3

To Cbz-protected *trans*-3-acetoxy-L-proline t butyl ester (1 mmol) in ethyl acetate (10 mL) was added 10% Pd/C and the reaction evacuated and flushed with hydrogen gas three times. The reaction was then stirred under a hydrogen atmosphere overnight, then filtered through a pad of celite and concentrated to dryness to afford the desired *trans*-3-acetoxy-L-proline t-butyl ester. MS (APCI negative) m/z 357 [M-H]. ^{1}H NMR (300 MHz, CD_3OD) Λ 4.0 (m, 2H), 3.75 (m, 2H), 3.10 (m, 1H), 2.85 (m, 1H), 2.40 (m, 2H), 2.2 (m, 2H), 2.0 (m, 2H), 1.65 to 1.0 (m, 15H), 0.90 (m, 3H).

Step 4

The title compound was prepared according to General Procedure A using *trans*-3-acetoxy-L-proline O-t-butyl ester and methyl 3-(*R*)-(*n*-butyl)propionate. The final treatment with hydroxylamine removed the acetyl group from the 3-hydroxy group of the proline.

Large-scale synthesis

Step 1

To *trans*-3-acetyloxy-L-proline t-butyl ester (11.8 mmol) in DCM (60 mL) was added *mono*-methyl 2-(*R*)-butylsuccinic acid (11.2 mmol), DIEA (23.6 mmol) and PyBOP (11.8 mmol) and the solution stirred for 16 h. The reaction was concentrated to an oil and purified on silica gel (Merck 60; hexanes/ethylacetate) to

afford 2.2 g of methyl 3-(*R*)-(*n*-butyl)-3-[(4-(*R*)-acetoxy-2-(*S*)-*tert*-butoxycarbonyl)pyrrolidin-1-ylcarbonyl]propionate as a clear oil **5** (50%).

Step 2

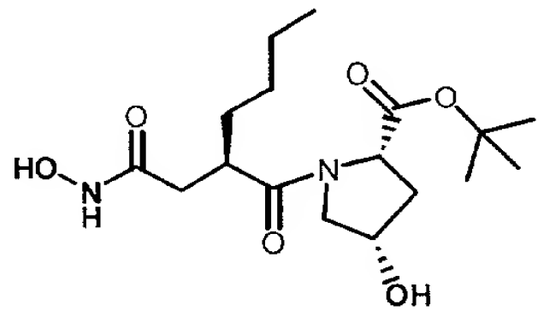
To methyl 3-(*R*)-(*n*-butyl)-3-[(4-(*R*)-acetoxy-2-(*S*)-*tert*-butoxycarbonyl)-pyrrolidin-1-ylcarbonyl]propionate (5.5 mmol) in methanol (25 mL) was added water (1 mL) and LiOH-H_2O (12.1 mmol) and the solution stirred 20 h. Standard aqueous work-up afforded 3-(*R*)-(*n*-butyl)-3-[(4-(*R*)-hydroxy-2-(*S*)-*tert*-butoxycarbonyl)-pyrrolidin-1-ylcarbonyl]propionic acid 2 g of a colorless oil which solidified upon standing (quant.).

Step 3

To a solution of 3-(*R*)-(*n*-butyl)-3-[(4-(*R*)-hydroxy-2-(*S*)-*tert*-butoxycarbonyl)-pyrrolidin-1-ylcarbonyl]propionic (5.51 mmol) in DCM (30 mL) was added O-benzylhydroxylamine-HCL (6.06 mmol), DIEA (13.3 mmol) and PyBOP and the solution stirred for 18 h. Standard aqueous work-up followed by silica gel chromatography (Merck 60; ethylacetate) afforded 1.14 g of the protected N-benzyloxy- 3-(*R*)-(*n*-butyl)-3-[(4-(*R*)-hydroxy-2-(*S*)-*tert*-butoxycarbonyl)pyrrolidin-1-ylcarbonyl]propionamide as a white gum (45%). This was dissolved in ethylacetate (50 mL), 5% Pd/C was added (110 mg), and a hydrogen atmosphere introduced. After 16 h the reaction was filtered through celite and concentrated to afford 810 mg of the title compound as a white foam (89%).

Example 18

Synthesis of *N*-hydroxy-3-(*R*)-(*n*-butyl)-3-[(4-(*S*)-hydroxy-2-(*S*)-*tert*-butoxycarbonyl)pyrrolidin-1-ylcarbonyl]propionamide

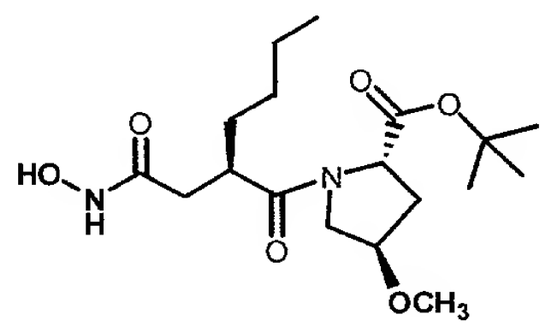


To methyl 3-(*R*)-(*n*-butyl)-3-[(4-(*R*)-hydroxy-2-(*S*)-*tert*-butoxycarbonyl)-pyrrolidin-1-ylcarbonyl]propionate (prepared by General Procedure A, omitting the final treatment with NH_2OH) in THF was added chloroacetic acid, TPP and DIAD

and the reaction stirred 18 h. The chloroacetate ester was purified on silica gel (Merck 60; hexanes/ethylacetate), dissolved in dioxane and then treated with aqueous 50% hydroxylamine. The reaction mixture was purified by preparative reverse-phase (C18) HPLC to afford the title compound. MS (APCI negative) m/z 357 [M-H].

Example 19

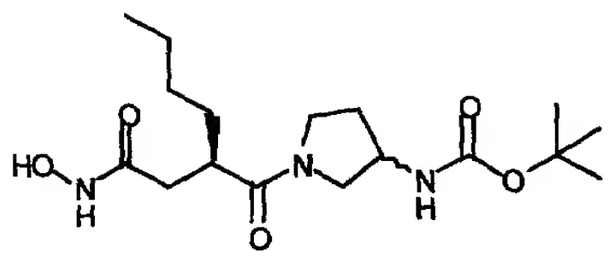
Synthesis of *N*-hydroxy-3-(*R*)-(*n*-butyl)-3-[(4-(*R*)-methoxy-2-(*S*)-*tert*-butoxycarbonyl)pyrrolidin-1-ylcarbonyl]propionamide



To methyl 3-(*R*)-(*n*-butyl)-3-[(4-(*R*)-hydroxy-2-(*S*)-*tert*-butoxycarbonyl)-pyrrolidin-1-ylcarbonyl]propionate in THF at 0 °C was added sodium hydride (60% dispersion in mineral oil) and the mixture stirred for 1 h. Iodomethane was added, and the reaction allowed to wam to rt and then stirred an additional 2 h. Standard aqueous work-up followed by purification on silica gel afforded the penultimate methyl ester. This was dissolved in dioxane and then treated with aqueous 50% hydroxylamine for 48 h. The reaction mixture was purified by preparative reverse-phase (C18) HPLC to afford the title compound. MS (APCI negative) m/z 371 [M-H].

Example 20

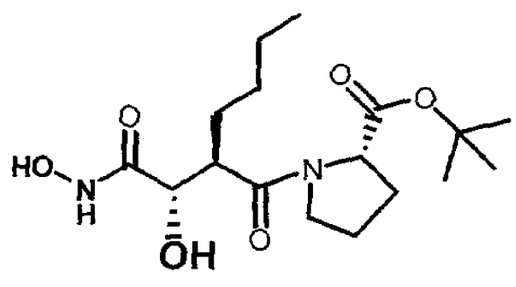
Synthesis of *N*-hydroxy-3-(*R*)-(*n*-butyl)-3-[3-(*RS*)-(*tert*-butoxycarbonyl-amino)pyrrolidin-1-ylcarbonyl]propionamide



The title compound was prepared according to General Procedure B from (±)-3-(N-Boc-amino)pyrrolidine (obtained from TCI America, Portland, Oregon) and *mono*-4-methyl 2-(*R*)-butylsuccinic acid. MS (APCI) m/z 358[M+H].

Example 21

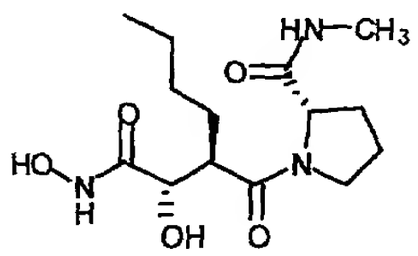
Synthesis of *N*-hydroxy-3-(*R*)-(*n*-butyl)-3-[2-(*S*)-(*tert*-butoxycarbonyl)pyrrolidin-1-ylcarbonyl]-2-(*S*)-hydroxypropionamide



The title compound was prepared according to General Procedure F or I . ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.93 (t, J= 7.5 Hz, 3 H), 1.31-1.49 (m, 4H), 1.44 (s, 9H), 1.76-2.23 (m, 6H), 3.23 (dt, J=2.5 and 7.5 Hz, 1H), 3.67-3.77 (m, 1H), 3.55-3.64 (m, 1H), 4.26 (d, J=2.5 Hz, 1H), 4.32 (dd, J=4.2 and 8.7 Hz, 1 H). ES-MS: calcd. For $C_{17}H_{30}N_2O_6$(358.43); found: 359 [M+1].

Example 22

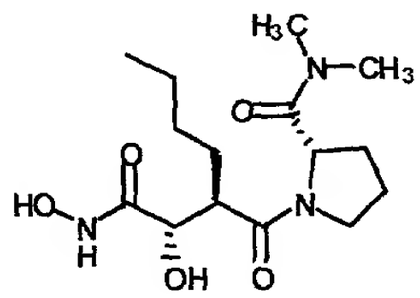
Synthesis of *N*-hydroxy-3-(*R*)-(*n*-butyl)-3-[2-(*S*)-(methylaminocarbonyl)pyrrolidin-1-ylcarbonyl]-2-(*S*)-hydroxypropionamide



The title compound was prepared according to General Procedure C from methylamine. MS (APCI negative) m/z 314 [M-H].

Example 23

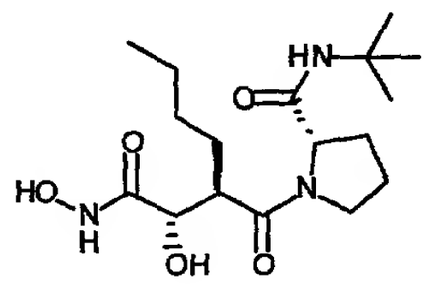
Synthesis of *N*-hydroxy-3-(*R*)-(*n*-butyl)-3-[2-(*S*)-(dimethylaminocarbonyl)pyrrolidin-1-ylcarbonyl]-2-(*S*)-hydroxypropionamide



The title compound was prepared according to General Procedure C from N,N-dimethylamine. MS (APCI negative) m/z 328 [M-H].

Example 24

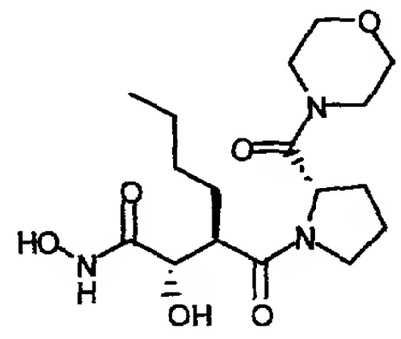
Synthesis of *N*-hydroxy-3-(*R*)-(*n*-butyl)-3-[2-(*S*)-(*tert*-butylaminocarbonyl)pyrrolidin-1-ylcarbonyl]-2-(*S*)-hydroxypropionamide



The title compound was prepared according to General Procedure C from *t*-butylamine. MS (APCI negative) m/z 356 [M-H].

Example 25

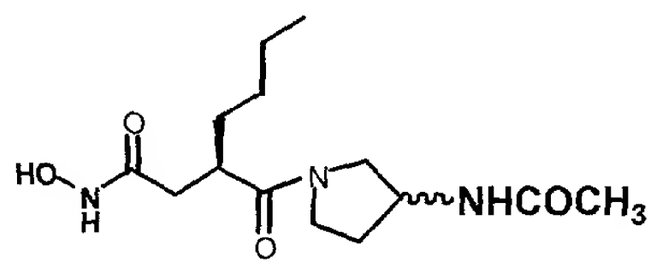
Synthesis of *N*-hydroxy-3-(*R*)-(*n*-butyl)-3-[2-(*S*)-(morpholin-4-ylcarbonyl)pyrrolidin-1-ylcarbonyl]-2-(*S*)-hydroxypropionamide



The title compound was prepared according to General Procedure C from morpholine. MS (APCI negative) m/z 370 [M-H].

Example 26

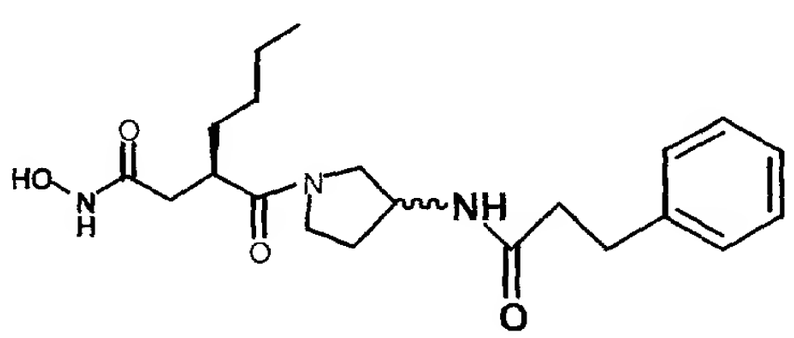
Synthesis of *N*-hydroxy-3-(*R*)-(*n*-butyl)-3-[3-(*RS*)-(acetylamino)pyrrolidin-1-yl-carbonyl]propionamide



To methyl 3-(*R*)-(*n*-butyl)-3-[3-(*RS*)-(*tert*-butoxycarbonylamino)pyrrolidin-1-ylcarbonyl]propionate, prepared from (±)-3-(N-*Boc*-amino)pyrrolidine (TCI America, Portland, Oregon) and *mono*-4-methyl 2-(*R*)-butylsuccinic acid, was added 4 N HCl in dioxane and the solution stirred for 4 h. The solution was evaporated to dryness, dissolved in dioxane, and then treated with acetic anhydride and pyridine and stirred for 2 h. Aqueous 50% hydroxylamine was added and the solution stirred for 2 d. The crude reaction mixture was purified by preparative reverse-phase (C18) HPLC to afford the title compound. MS (APCI negative) m/z 298 [M-H].

Example 27

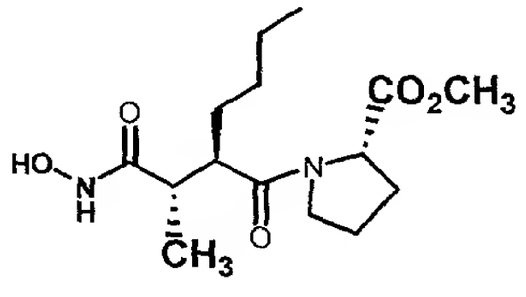
Synthesis of *N*-hydroxy-3-(*R*)-(*n*-butyl)-3-[3-(*RS*)-(2-phenylethylcarbonylamino)-pyrrolidin-1-ylcarbonyl]propionamide



To methyl 3-(*R*)-(*n*-butyl)-3-[3-(*RS*)-(*tert*-butoxycarbonylamino)pyrrolidin-1-ylcarbonyl]propionate, prepared from (±)-3-(N-Boc-amino)pyrrolidine and *mono*-4-methyl 2-(*R*)-butylsuccinic acid, was added 4 N HCl in dioxane and the solution stirred for 4 h. The solution was evaporated to dryness, dissolved in dioxane, and then treated with 3-phenylpropionic acid, DIEA, and HATU and stirred for 2 h. Aqueous 50% hydroxylamine was added and the solution stirred for 2 d. The crude reaction mixture was purified by preparative reverse-phase (C18) HPLC to afford the title compound.

Example 28

Synthesis of *N*-hydroxy-3-(*R*)-(*n*-butyl)-3-[2-(*S*)-(methoxycarbonyl)pyrrolidin-1-ylcarbonyl]-2-(*S*)-methylpropionamide



Step 1

To mono *t*-butyl 2-(*R*)-(*n*-butyl)succinic acid (2.0 g, 8.70 mmol; prepared in three steps from hexanoylchloride using the procedure of Example 16, Step A for the synthesis of monomethyl-2-R-butylsuccinic acid, with substitution of *t*-butyl bromoacetate for methyl bromoacetate) in anhydrous THF (40 mL) at –78 °C was added LDA (2.2 eq., 19.1 mmol, 9.56 ml of a 2.0 M solution in THF/hexane/ethyl-benzene) and the reaction stirred for 1 h. Iodomethane (11.3 mmol, 1.6 g) was then added and the reaction allowed to warm to room temperature over 2 h. The solution was quenched with methanol (ca. 5 mL), evaporated to dryness, and the residue dissolved in ethylacetate (50 mL). This solution was extracted with saturated sodium bicarbonate (3 x 30 mL), the combined aqueous layers acidified to pH 3 with 1 N HCl, and these were extracted with ethylacetate (3 x 50 mL). The combined organic layers were dried (Na_2SO4), concentrated, and purified by silica gel chromatography (Merck 60; 95:5 DCM/methanol) to afford mono *t*-butyl 2-(*R*)-(*n*-butyl)-3-(*RS*)-methylsuccinic acid as a light orange oil (1.25 g). The ratio of R/S diastereomers was > 6:1.

Step 2

An aliquot of mono *t*-butyl 2-(*R*)-(*n*-butyl)-3-(*RS*)-methylsuccinic acid (1.0 g, 4.10 mmol) was epimerized by first dissolving it in THF (22 mL), cooling to – 78 °C and then adding LDA (9.02 mmol, 4.52 mL of a 2.0 M solution). The solution was allowed to warm to rt over 2 hours, then cooled back down to –78 °C and quenched with methanol (1.7 mL). This epimerization procedure was repeated once more, then an aqueous work-up was performed as described above to afford 700 mg of mono *t*-butyl 2-(*R*)-(*n*-butyl)-3-(*RS*)-methylsuccinic acid. ^{1}H NMR analysis of this product suggested approximately 2:1 ratio of R/S diastereomers.

Step 3

To mono *t*-butyl 2-(*R*)-(*n*-butyl)-3-(*RS*)-methylsuccinic acid (680 mg, 1.39 mmol, prepared in step 2 above) in DCM (15 mL) was added L-proline methyl ester hydrochloride (3.34 mmol, 554 mg), DIEA (1.28 mL, 7.34 mmol) and then PyBOP (1.74 g, 3.34 mmol). The reaction was stirred for 16 h, concentrated to dryness, and then purified via silica gel chromotography (1:1 hexanes/ethylacetate) to afford mono *t*-butyl 3-(*R*)-(*n*-butyl)-3-[2-(*S*)-methoxycarbonyl)pyrrolidin-1-ylcarbonyl]-2-(*S*)-methylpropionate (260 mg).

Step 4

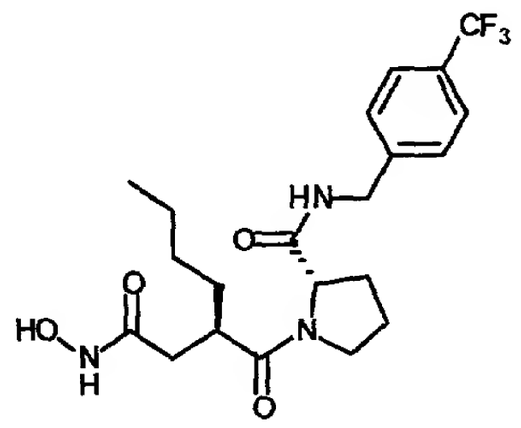
The *t*-butyl group was removed from mono *t*-butyl 3-(*R*)-(*n*-butyl)-3-[2-(*S*)-methoxycarbonyl)pyrrolidin-1-ylcarbonyl]-2-(*S*)-methylpropionate (260 mg, 732 μmol) using 1:2 TFA/DCM, followed by evaporation of the TFA and solvent. To the resulting product in DCM (5 mL) at 0 °C was added O-benzylhydroxylamine hydrochloride (129 mg, 805 μmol), HOBt (112 mg, 732 μmol), DIEA (708 μL, 1.61 mmol) and then solid EDC (154 mg, 805 μmol) and the reaction allowed to warm to rt and then stirred overnight. The reaction was evaporated to dryness, and purified on a silica gel column (1:1 hexanes/ethylacetate) to afford *N*-benzyloxy-3-(*R*)-(*n*-butyl)-3-[2-(*S*)-methoxycarbonyl)pyrrolidin-1-ylcarbonyl]-2-(*S*)-methylpropionamide as a colorless glass (212 mg).

Step 5

To *N*-benzyloxy- 3-(*R*)-(*n*-butyl)-3-[2-(*S*)-methoxycarbonyl)pyrrolidin-1-ylcarbonyl]-2-(*S*)-methylpropionamide (40 mg) in methanol (3 mL) was added 10% Pd/C (10 mg). The reaction was evacuated briefly under high-vacuum, and the atmosphere replaced with 1 atm hydrogen gas (balloon). This procedure was repeated twice more, then the suspension was stirred under H_2 gas for 3 h. The reaction was then filtered through a plug of celite to afford the title compound as a clear, colorless gum (31 mg). MS (APCI) m/z 315 [M+H].

Example 29

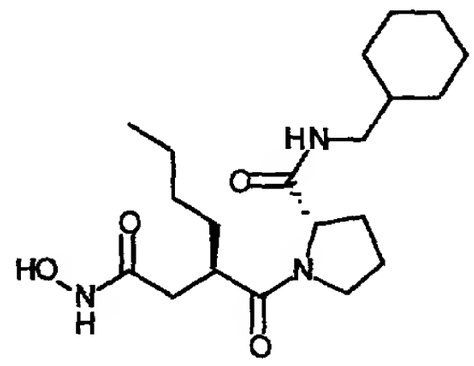
Synthesis of *N*-hydroxy-3-(*R*)-(*n*-butyl)-3-[2-(*S*)-(3-trifluoromethylbenzylamino-carbonyl)pyrrolidin-1-ylcarbonyl]propionamide



The title compound was prepared according to General Procedure D from L-proline-(4-trifluoromethyl)benzylamide. MS (APCI) m/z 444 [M+H].

Example 30

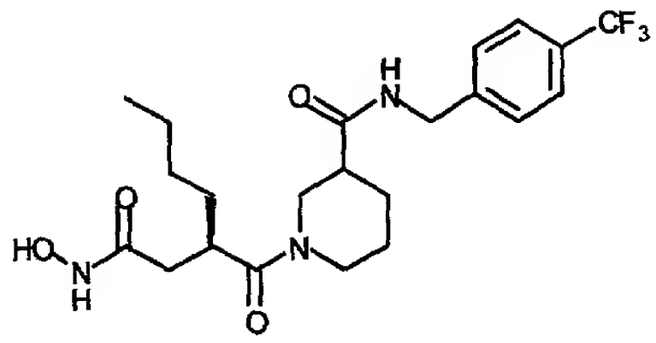
Synthesis of *N*-hydroxy-3-(*R*)-(*n*-butyl)-3-[2-(*S*)-(cyclohexylmethylaminocarbonyl)-pyrrolidin-1-ylcarbonyl]propionamide



The title compound was prepared according to General Procedure A from *mono*-methyl 2-(*R*)-butylsuccinic acid and L-proline-(cyclohexyl)methylamide. MS (APCI) m/z 382 [M+H].

Example 31

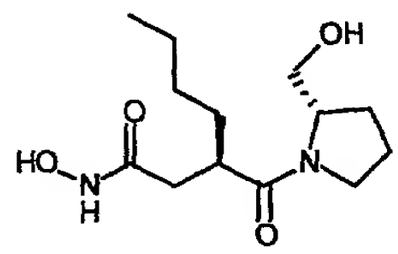
Synthesis of *N*-hydroxy-3-(*R*)-(*n*-butyl)-3-[3-(*RS*)-((4-trifluoromethylbenzyl)-aminocarbonyl)piperidin-1-ylcarbonyl]propionamide



The title compound was prepared according to General Procedure A from *mono*-methyl 2-(*R*)-butylsuccinic acid and (±)-3-carboxypiperidine-(4-trifluoromethylbenzyl)amide. MS (APCI) m/z 458 [M+H].

Example 32

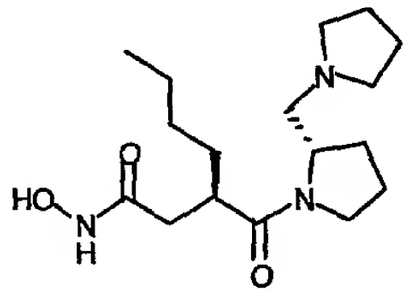
Synthesis of *N*-hydroxy-3-(*R*)-(*n*-butyl)-3-[(2-(*S*)-(hydroxymethyl)-pyrrolidin-1-ylcarbonyl]propionamide



The title compound was prepared according to General Procedure A from *mono*-methyl 2-(*R*)-butylsuccinic acid and L-prolinol. MS (APCI) m/z 273[M+H].

Example 33

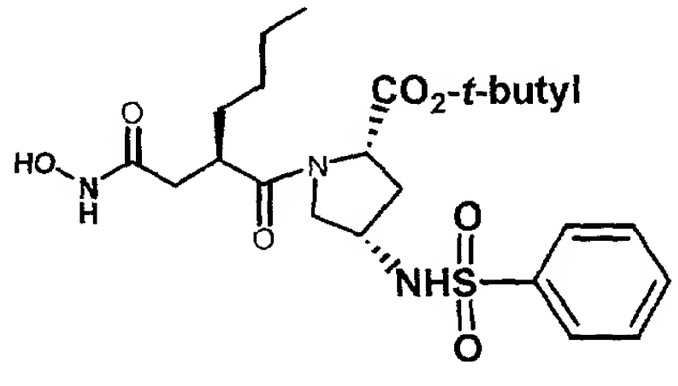
Synthesis of *N*-hydroxy-3-(*R*)-(*n*-butyl)-3-[(2-(*S*)-(pyrrolidin-1-ylmethyl)-pyrrolidin-1-ylcarbonyl]propionamide



The title compound was prepared according to General Procedure A from *mono*-methyl 2-(*R*)-butylsuccinic acid and (*S*)-2-(*N*-pyrrolidinylmethyl)-pyrrolidine. MS (APCI) m/z 326 [M+H].

Example 34

Synthesis of *N*-hydroxy-3-(*R*)-(*n*-butyl)-3-[4-(S)-(phenylsulfonamido)-2-(*S*)-(tert-butyloxycarbonyl)pyrrolidin-1-ylcarbonyl]propionamide



Step 1

To mono methyl 3-(*R*)-(*n*-butyl)-3-[2-(*S*)-*tert*-butoxycarbonyl)-4-(*R*)-hydroxypyrrolidin-1-ylcarbonyl]propionate (1.4g, 3.92 mmol; prepared according to General Procedure A from methyl 2-(*R*)-butylsuccinic acid and *trans*-L-hydroxy-proline *tert*-butyl ester) in DCM at –20°C was slowly added methanesulfonyl chloride ($MeSO_2Cl$) (0.62mL, 7.84 mmol) and the reaction stirred 4 h. DCM was removed *in vacuo*, and the residue was dissolved in EtOAc (100 mL), washed with saturated $NaHCO_3$, dilute HCl (5%) and brine and then dried ($MgSO_4$). Concentration *in vacuo* afforded methyl 3-(*R*)-(*n*-butyl)-3-[2-(*S*)-*tert*-butoxycarbonyl)-4-(*R*)-mesyloxy-pyrrolidin-1-ylcarbonyl]propionate which was used directly without further purification.

Step 2

To methyl 3-(*R*)-(*n*-butyl)-3-[2-(*S*)-*tert*-butoxycarbonyl)-4-(*R*)-mesyloxy-pyrrolidin-1-ylcarbonyl]propionate in DMF (30 mL) was added NaN_3 (2.6g) and the resulting solution heated at 65°C for 48. The DMF was removed *in vacuo* and the residue was purified by silica gel column chromatography to afford 1.3 gram of the desired methyl 3-(*R*)-(*n*-butyl)-3-[2-(*S*)-*tert*-butoxycarbonyl)-4-(*S*)-azido-pyrrolidin-1-ylcarbonyl]propionate.

Step 3

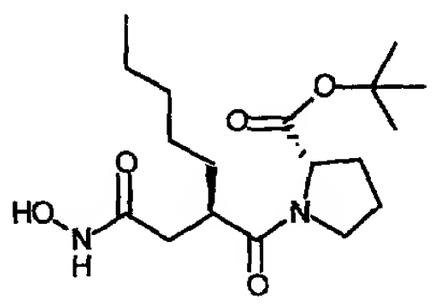
Methyl 3-(*R*)-(*n*-butyl)-3-[2-(*S*)-*tert*-butoxycarbonyl)-4-(*S*)-azido-pyrrolidin-1-ylcarbonyl]propionate (1.3 g, 3.4 mmol) was hydrogenated at rt with Pd-C (10%) for 18 h. The reaction was filtered through a pad of celite, and washed with EtOAc. Concentration of the filtrate yielded 1.2 g of methyl 3-(*R*)-(*n*-butyl)-3-[2-(*S*)-*tert*-butoxycarbonyl)-4-(*S*)-aminopyrrolidin-1-ylcarbonyl]propionate.

Step 4

Phenylsulfonyl chloride (2 eq.) was added slowly to a solution of methyl 3-(*R*)-(*n*-butyl)-3-[2-(*S*)-*tert*-butoxycarbonyl)-4-(*S*)-azido-pyrrolidin-1-ylcarbonyl]-propionate (ca. 0.1 g) in DCM (1mL) and pyridine (0.1 mL) at 0 °C. The solution was allowed to warm to rt and then stirred an additional 2 h. The solvent was removed *in vacuo*, the residue dissolved in EtOAc (5 mL) and washed with HCl solution (5%), $NaHCO_3$ (sat.) and brine. Concentration *in vacuo* gave the crude methyl 3-(*R*)-(*n*-butyl)-3-[2-(*S*)-*tert*-butoxycarbonyl)-4-(*S*)-phenylsulfonamido-pyrrolidin-1-ylcarbonyl]propionate which was directly converted to the corresponding hydroxamate by treatment with aqueous 50% NH_2OH (1 mL) and dioxane (2 mL) at rt for 3 days. The final product *N*-hydroxy-3-(*R*)-(*n*-butyl)-3-[4-(S)-(phenylsulfonamido)-2-(*S*)-(tert-butyloxycarbonyl)pyrrolidin-1-ylcarbonyl]-propionamide was purified by preparative HPLC. ^1H NMR (CD_3OD): δ 7.90 (m, 2H), 7.60 (m, 3H), 4.15(t, J=7.9 Hz, 1H), 4.0 (m, 1H), 3.90 (m, 1H), 3.25(m, 1H), 2.90 (m, 1H), 2.35 (m, 2H), 2.15 (m, 3H), 1.75(m, 1H), 1.60 to 1.20 (m, 13H), 0.90 ppm (s, 3H); MS (APCI negative) m/z 496 [M-1].

Example 35

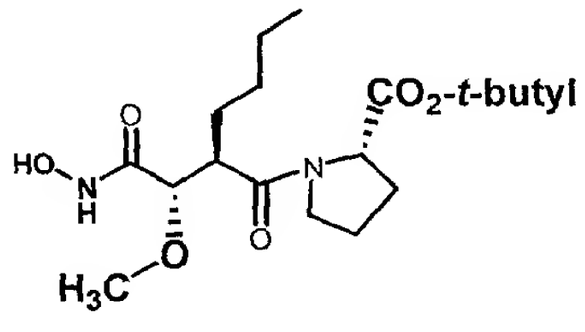
Synthesis of *N*-hydroxy-3-(*R*)-(*n*-pentyl)-3-[(2-(*S*)-(*tert*-butoxycarbonyl)-pyrrolidin-1-ylcarbonyl]propionamide



The title compound was prepared according to General Procedure A from *mono*-methyl 2-(*R*)-pentylsuccinic acid and L-proline t-butyl ester. MS (APCI) m/z 357 [M+H].

Example 36

Synthesis of *N*-hydroxy-3-(*R*)-(*n*-butyl)-3-[(2-(*S*)-(*tert*-butoxycarbonyl)-pyrrolidin-1-ylcarbonyl]-2-(*S*)-methoxypropionamide



Step 1

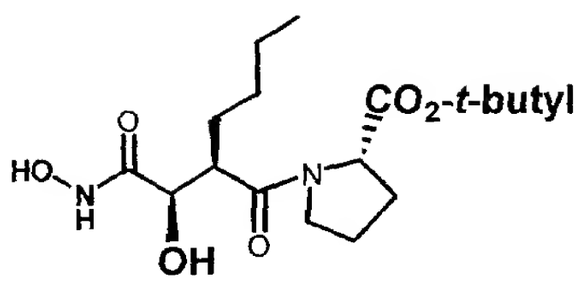
To 1-(2,2-dimethyl-4-oxo-1,3-dioxolan-5-yl)-1-(2-(*S*)-tert-butoxycarbonylpyrrolidin-1-ylcarbonyl)pentane (4 mmol; prepared as described previously using, *tert*-butyl ester of compound F-6, General Procedure F) in methanol (20 mL) was added 1m MeONa (1ml) and stirred for 1 h. The reaction was neutralized with H^+ resin , filtered, and the filtrate was concentrated to dryness. The residue purified on silica gel to afford methyl 3-(*R*)-(*n*-butyl)-3-[(2-(*S*)-(*tert*-butoxycarbonyl)-pyrrolidin-1-ylcarbonyl]-2-(*S*)-hydroxypropionate.

Step 2

To a solution of methyl 3-(*R*)-(*n*-butyl)-3-[(2-(*S*)-(*tert*-butoxycarbonyl)-pyrrolidin-1-ylcarbonyl]-2-(*S*)-hydroxypropionate (1 mmol) in DMF (10 ml) was added NaH. After 30 minutes, methyl iodide (3 mmol) was added and the solution stirred an additional hour. The reaction was then diluted with ethyl acetate, washed with water, dried with Na_2SO_4, filtered and concentrated. The crude methyl ether was dissolved in dioxane, treated with aqueous 50% hydroxylamine, and stirred for two days. The crude reaction mixture was purified by preparative reverse-phase (C18) HPLC to afford the title compound. MS (APCI negative) m/z 371 [M-H].

Example 37

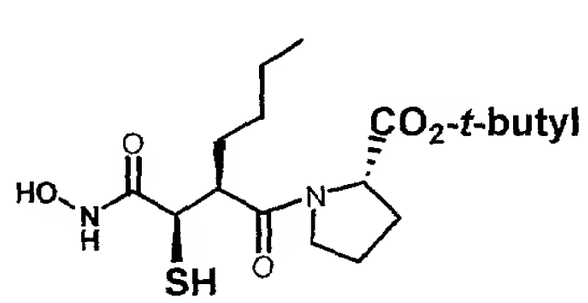
Synthesis of *N*-hydroxy-3-(*R*)-(*n*-butyl)-3-[(2-(*S*)-(*tert*-butoxycarbonyl)-pyrrolidin-1-ylcarbonyl]-2-(*R*)-hydroxypropionamide



To a solution of triflic anhydride (1.2 mmol) in CH_2Cl_2 (5 ml) at –15°C was added pyridine (2.5 mmol) followed by the addition of a solution of methyl 3-(*R*)-(*n*-butyl)-3-[(2-(*S*)-(*tert*-butoxycarbonyl)pyrrolidin-1-ylcarbonyl]-2-(*S*)-hydroxy-propionate (1 mmol, see Example 36 for preparation) in dichloromethane. The reaction was allowed to warm to –5°C over 1 hour, then the solution was washed with aqueous 10% citric acid, water and sodium bicarbonate solutions, then dried (Na_2SO_4) and concentrated. This residue was dissolved in toluene (10 ml) and treated with tetrabutylammonium benzoate (TBAB, 2 mmol) for 1 hour. After removal of solvent, the residue was purified on silica gel (hexanes/ethylacetate) to afford methyl 3-(*R*)-(*n*-butyl)-3-[(2-(*S*)-(*tert*-butoxycarbonyl)pyrrolidin-1-ylcarbonyl]-2-(*R*)-benzoyloxy-propionate. Treatment of this intermediate with aqueous hydroxylamine/dioxane solution for 2 days, followed by purification via semi-preparative HPLC provided title compound. MS (APCI) m/z 359 [M+H].

Example 38

Synthesis of *N*-hydroxy-3-(*S*)-(*n*-butyl)-3-[(2-(*S*)-(*tert*-butoxycarbonyl)-pyrrolidin-1-ylcarbonyl]-2-(*R*)-thiolpropionamide

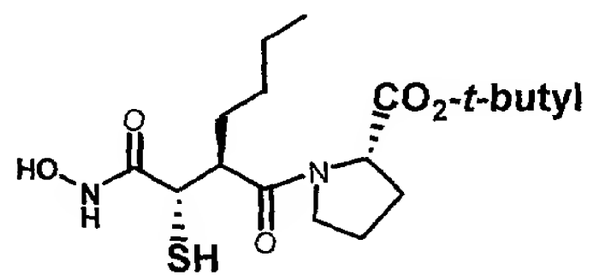


To methyl 3-(*R*)-(*n*-butyl)-3-[(2-(*S*)-(*tert*-butoxycarbonyl)pyrrolidin-1-yl-carbonyl]-2-(*S*)-hydroxypropionate (*see* Example 36 for preparation) in THF is added triphenylphosphine (TPP), diisopropylazodicarboxylate (DIAD) and thioacetic acid and the solution stirred overnight. Aqueous work-up and purification on silica gel affords methyl 3-(*S*)-(*n*-butyl)-3-[(2-(*S*)-(*tert*-butoxycarbonyl)pyrrolidin-1-

ylcarbonyl]-2-(*R*)-acetylthiopropionate. This compound was dissolved in degassed dioxane and aqueous 50% hydroxylamine, then stirred for 2 d. The crude reaction mixture was purified by preparative reverse-phase (C18) HPLC to afford the title compound.

Example 39

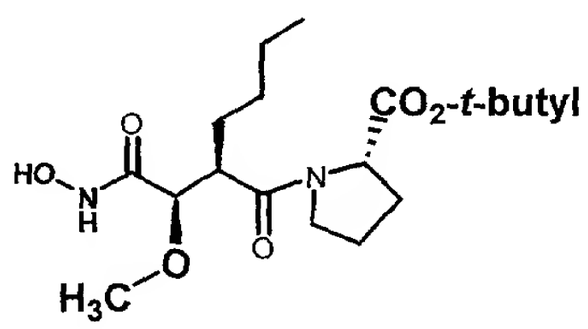
Synthesis of *N*-hydroxy-3-(*S*)-(*n*-butyl)-3-[(2-(*S*)-(*tert*-butoxycarbonyl)-pyrrolidin-1-ylcarbonyl]-2-(*S*)-thiolpropionamide



To a solution of triflic anhydride (Tf_2O, 1.2 mmol) in CH_2Cl_2 (5 ml) at –15°C was added pyridine (2.5 mmol) followed by the addition of a solution of methyl 3-(*R*)-(*n*-butyl)-3-[(2-(*S*)-(*tert*-butoxycarbonyl)pyrrolidin-1-yl-carbonyl]-2-(*R*)-hydroxypropionate (1 mmol, prepared as described in Example 40, below) in DCM. The reaction was allowed to warm to –5°C over 1 hr, then the solution was washed with aqueous 10% citric acid, water, and sodium bicarbonate solution, then dried (Na_2SO_4) and concentrated. This residue was dissolved in THF (5 ml) and treated with potassium thioacetate (2 mmol) for 1 h. After removal of solvent, the residue was purified on silica gel (hexanes/ethyl acetate) to afford methyl 3-(*R*)-(*n*-butyl)-3-[(2-(*S*)-(*tert*-butoxycarbonyl)pyrrolidin-1-yl-carbonyl]-2-(*S*)-acetylthiopropionate. Treatment of this compound with aqueous hydroxylamine/dioxane solution for 2 days, followed by purification via semi-preparative HPLC, provided the title compound. MS(APCI) m/z 375 [M+H].

Example 40

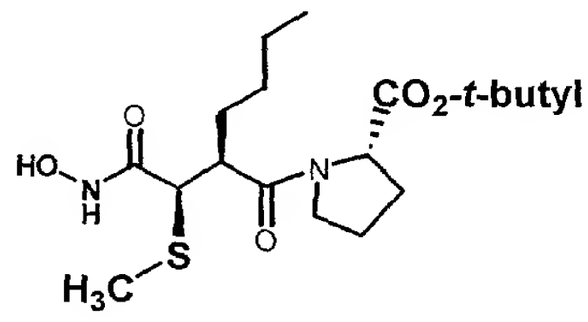
Synthesis of *N*-hydroxy-3-(*R*)-(*n*-butyl)-3-[(2-(*S*)-(*tert*-butoxycarbonyl)-pyrrolidin-1-ylcarbonyl]-2-(*R*)-methoxypropionamide



Methyl 3-(*R*)-(*n*-butyl)-3-[(2-(*S*)-(*tert*-butoxycarbonyl)pyrrolidin-1-yl-carbonyl]-2-(*R*)-benzoyloxypropionate (prepared as described in Example 37) was de-O-benzoylated by treatment with methanolic sodium methoxide at 0°C for 2 hours. The solution was neutralized with IR-120 (H^+) resin, filtered, concentrated and purified on silica gel (hexanes/ethyl acetate) to afford methyl 3-(*R*)-(*n*-butyl)-3-[(2-(*S*)-(*tert*-butoxycarbonyl)pyrrolidin-1-yl-carbonyl]-2-(*R*)-hydroxypropionate. To a solution of methyl 3-(*R*)-(*n*-butyl)-3-[(2-(*S*)-(*tert*-butoxycarbonyl)pyrrolidin-1-yl-carbonyl]-2-(*R*)-hydroxypropionate in DMF at 0°C was added sodium hydride and the reaction stirred for 1 hour. Methyl iodide was added and the reaction stirred for 1 hour at 0°C, then allowed to warm to rt and stirred an additional 2 h. Conventional aqueous workup afforded the intermediate ether, which was treated with dioxane/aqueous hydroxylamine followed by purification via semi-preparative HPLC to afford the title compound. MS (APCI) m/z 373 [M+H].

Example 41

Synthesis of *N*-hydroxy-3-(*S*)-(*n*-butyl)-3-[(2-(*S*)-(*tert*-butoxycarbonyl)-pyrrolidin-1-ylcarbonyl]-2-(*R*)-methylthiopropionamide

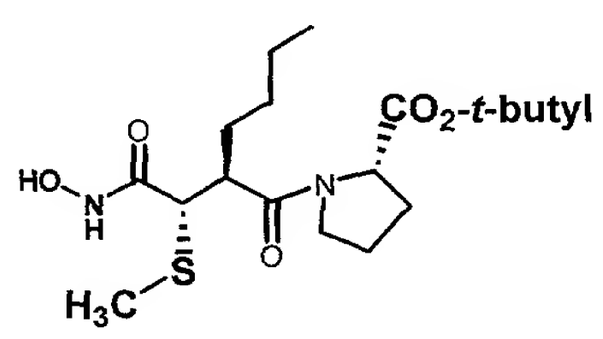


To a solution of triflic anhydride (1.2 mmol) in CH_2Cl_2 (5 ml) at –15°C is added pyridine (2.5 mmol) followed by the addition of a solution of methyl 3-(*R*)-(*n*-butyl)-3-[(2-(*S*)-(*tert*-butoxycarbonyl)pyrrolidin-1-yl-carbonyl]-2-(*S*)-hydroxy-

propionate (prepared as described in Example 36 above; 1 mmol) in dichloromethane. The solution is concentrated to dryness, dissolved in DMF and then treated with sodium thiomethoxide. Aqueous work-up followed by purification on silica gel affords methyl 3-(*S*)-(*n*-butyl)-3-[(2-(*S*)-(*tert*-butoxycarbonyl)pyrrolidin-1-yl-carbonyl]-2-(*R*)-methylthiopropionate which is dissolved in dioxane, treated with aqueous 50% hydroxylamine, and then stirred for 2 d. The crude reaction mixture is purified by preparative reverse-phase (C18) HPLC to afford title compound.

Example 42

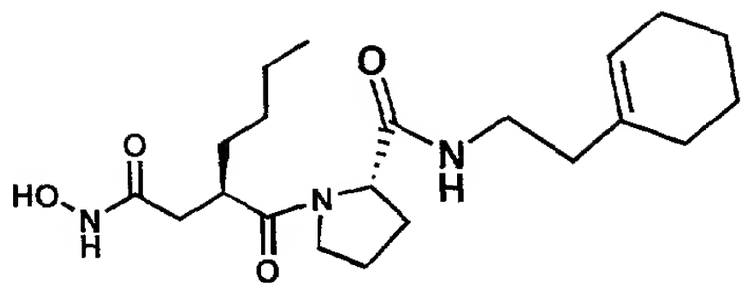
Synthesis of *N*-hydroxy-3-(*S*)-(*n*-butyl)-3-[(2-(*S*)-(*tert*-butoxycarbonyl)-pyrrolidin-1-ylcarbonyl]-2-(*S*)-methylthiopropionamide



To a solution of triflic anhydride (1.2 mmol) in CH_2Cl_2 (5 ml) at −15°C is added pyridine (2.5 mmol) followed by the addition of a solution of methyl 3-(*R*)-(*n*-butyl)-3-[(2-(*S*)-(*tert*-butoxycarbonyl)pyrrolidin-1-yl-carbonyl]-2-(*R*)-hydroxy-propionate (prepared as described in Example 40; 1 mmol) in dichloromethane. The solution is concentrated to dryness, dissolved in DMF and then treated with sodium thiomethoxide. Aqueous work-up followed by purification on silica gel affords methyl 3-(*S*)-(*n*-butyl)-3-[(2-(*S*)-(*tert*-butoxycarbonyl)pyrrolidin-1-yl-carbonyl]-2-(*S*)-methylthiopropionate which is dissolved in dioxane, treated with aqueous 50% hydroxylamine, and then stirred for 2 d. The crude reaction mixture is purified by preparative reverse-phase (C18) HPLC to afford the title compound.

Example 43

Synthesis of *N*-hydroxy-3-(*R*)-(*n*-butyl)-3-[(2-(*S*)-(2-cyclohex-1-enylethyl-aminocarbonyl)pyrrolidin-1-ylcarbonyl]propionamide



Step 1

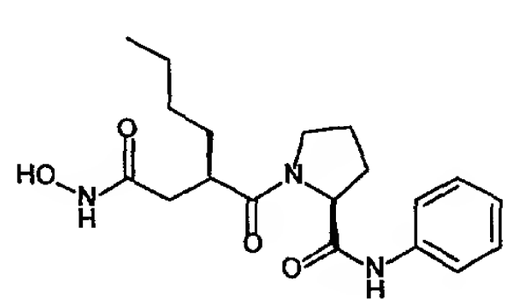
To methyl 3-(*R*)-(*n*-butyl)-3-[(2-(*S*)-(*tert*-butoxycarbonyl)pyrrolidin-1-yl-carbonyl]propionate (1 mmol; prepared in one step from *mono*-4-methyl 2-(*R*)-butylsuccinic acid and L-proline *t*-butyl ester) was added 1 M HCl in dioxane (5 mL) and the solution stirred 4 h. Conventional aqueous workup afforded methyl 3-(*R*)-(*n*-butyl)-3-[(2-(*S*)-(carboxy)pyrrolidin-1-yl-carbonyl]propionate.

Step 2

To methyl 3-(*R*)-(*n*-butyl)-3-[(2-(*S*)-(carboxy)pyrrolidin-1-yl-carbonyl]propionate (0.2 mmol) in dioxane (1 mL) was added 2-(1-cyclohexenyl)-ethyl amine (0.22 mmol), DIEA (0.22 mmol) and HATU (0.22 mmol) and the reaction stirred for 2 h. Aqueous 50 % hydroxylamine was then added (1 mL), and the reaction stirred an additional 24 h. The reaction mixture was purified by preparative reverse-phase (C18) HPLC to afford the title compound. MS (APCI) m/z 394 [M+H].

Example 44

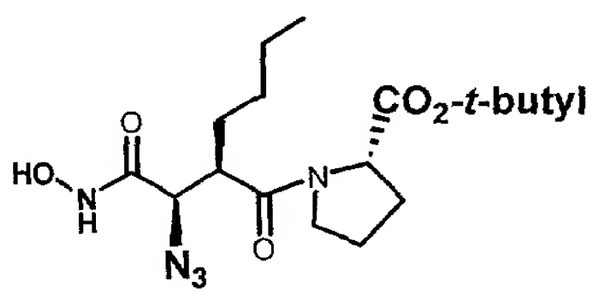
Synthesis of *N*-hydroxy-3-(*R*)-(*n*-butyl)-3-[(2-(*S*)-(phenylaminocarbonyl)-pyrrolidin-1-ylcarbonyl]propionamide



The title compound was prepared as described in Example 43, above, using aniline in place of 2-(1-cyclohexenyl)ethylamine. MS (APCI) m/z 362 [M+H].

Example 45

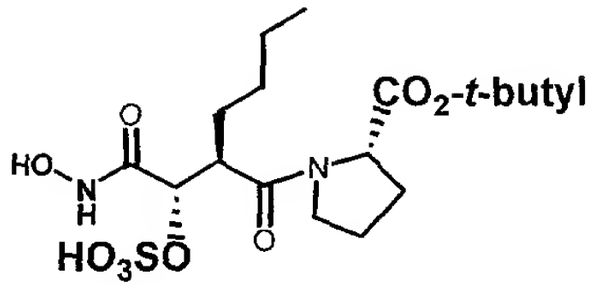
Synthesis of *N*-hydroxy-3-(*R*)-(*n*-butyl)-3-[2-(*S*)-(*tert*-butoxycarbonyl)-pyrrolidin-1-carbonyl]-2-(*R*)-azidopropionamide



To a solution of methyl 3-(*R*)-(*n*-butyl)-3-[(2-(*S*)-(*tert*-butoxycarbonyl)-pyrrolidin-1-ylcarbonyl]-2-(*S*)-hydroxypropionate (intermediate **G-3** from General Procedure G, 2 mmol) in DCM (10 mL) was added pyridine (6 mmol), the reaction was cooled to –20 °C, then triflic anhydride (4 mmol) was added. The solution was stirred for 1 hour and after the usual work-up was concentrated, resuspended in DMF (10 mL), and treated with sodium azide (2.5 mmol). The reaction was stirred for 16 h, then diluted with ethylacetate, washed with water, saturated aqueous sodium bicarbonate, and brine, then dried (Na_2SO_4) and puriifed on silica gel (ethylacetate/hexanes) to afford methyl 3-(*R*)-(*n*-butyl)-3-[(2-(*S*)-(*tert*-butoxycarbonyl)-pyrrolidin-1-ylcarbonyl]-2-(*R*)-azidopropionate. To a solution of the azido compound (0.5 mmol) in dioxane (2 mL) was added aqueous 50 % hydroxylamine (1 mL) and the reaction stirred for 48 h. The crude reaction mixture was then purified by preparative reverse-phase (C18) HPLC to afford the title compound. ^{1}H NMR(CDCl3): δ 4.28-4.24 (dd, J = 5.1 & 4.6Hz, 1H), 3.92 (d, J = 9.8 Hz,1H), 3.80-3.74 (m, 1H), 3.64-3.57 (m, 1H), 3.16-3.09 (m, 1H), 2.22-1.91 (m, 4H), 1.89-1.76 (m, 2H), 1.43 (s, 9H), 1.40-1.35 (m, 4H), 0.92 (t, J = 6.7 Hz). ES-MS: calcd. For $C_{17}H_{29}N_5O_5$ (383.3); found: 384 [M+1].

Example 46

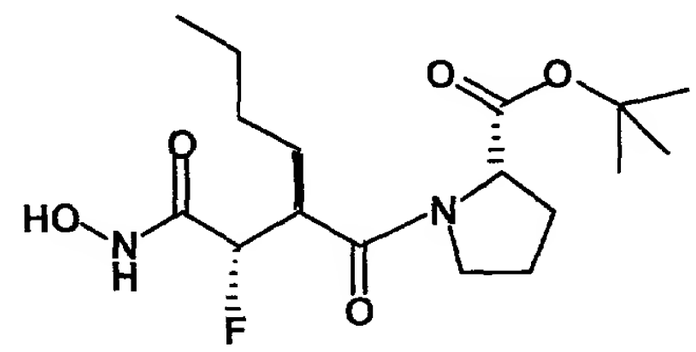
Synthesis of *N*-hydroxy-3-(*S*)-(*n*-butyl)-3-[2-(*S*)-(*tert*-butoxycarbonyl)-pyrrolidin-1-carbonyl]-2-(*S*)-sulfonyloxypropionamide



To a solution of methyl 3-(*R*)-(*n*-butyl)-3-[(2-(*S*)-(*tert*-butoxycarbonyl)-pyrrolidin-1-ylcarbonyl]-2-(*S*)-hydroxypropionate (intermediate **G-3** from General Procedure G, 2 mmol) in DMF (10 mL) was added pyridinium sulfurtrioxide (2.2 mmol) and the solution stirred for 1 h. The reaction was diluted with ethylacetate and washed with saline, dried (Na_2SO_4) and concentrated to afford methyl 3-(*S*)-(*n*-butyl)-3-[(2-(*S*)-(*tert*-butoxycarbonyl)-pyrrolidin-1-ylcarbonyl]-2-(*S*)-sulfonyloxypropionate. This sulfonyloxy compound was dissolved in dioxane, treated with aqueous 50 % hydroxylamine (1 mL) and the reaction stirred for 48 h. The crude reaction mixture was then purified by preparative reverse-phase (C18) HPLC to afford the title compound. ^{1}H NMR ($CDCl_3$): δ 4.63 (m, 2H), 4.19-3.82 (m, 2H), 3.79-3.67 (m, 1H), 2.36-1.83 (m, 4H), 1.81-1.59 (2H), 1.45 (s, 9H), 1.34-1.26 (m, 2H), 0.89 (t, J = 6.3 Hz). ES-MS: calcd. For $C_{17}H_{30}N_2O_9S$ (438.49); found: 439.2 [M+1].

Example 47

Synthesis of *N*-hydroxy-3-(*S*)-(*n*-butyl)-3-[2-(*S*)-(*tert*-butoxycarbonyl)-pyrrolidin-1-carbonyl]-2-(*S*)-fluoropropionamide

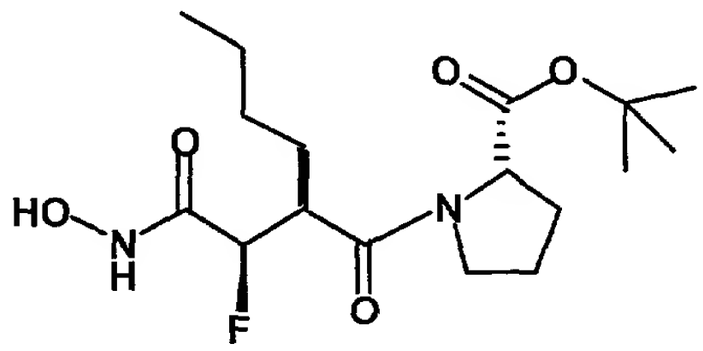


The title compound was prepared by treatment of methyl 3-(*S*)-(*n*-butyl)-3-[(2-(*S*)-(*tert*-butoxycarbonyl)pyrrolidin-1-ylcarbonyl]-2-(*S*)-fluoropropionate (intermediate H-**4**, General Procedure H), with aqueous 50 % hydroxylamine followed by purification on preparative reverse-phase (C18) HPLC. ^{1}H NMR ($CDCl_3$) δ 5.16-4.98 (dd, $J_{H2,3}$ = 6.8 Hz & $_{JH,F}$ = 47 Hz, 1H), 4.39-4.35 (dd, J = 4.4 & 3.8 Hz, 1H), 3.78 (m, 1H), 3.66-3.61 (m, 1H), 3.31-3.22 (m, 1H), 2.24-1.91 (m, 4H),

1.77-1.70 (m, 2H), 1.44 (s, 9H), 1.40-1.23 (m, 4H), 0.89 (t, J = 6.9 & 7.2 Hz). ES-MS: calcd. For $C_{17}H_{29}FN_2O_5$ (360.42); found: 361 [M+1].

Example 48

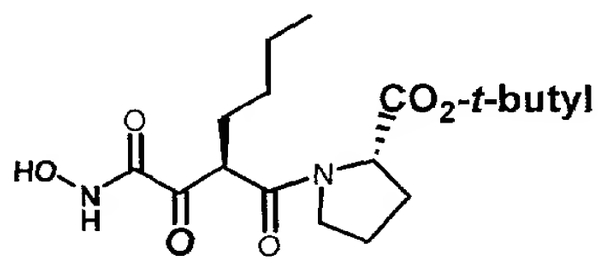
Synthesis of *N*-hydroxy-3-(*S*)-(*n*-butyl)-3-[2-(*S*)-(*tert*-butoxycarbonyl)-pyrrolidin-1-carbonyl]-2-(*R*)-fluoropropionamide



The title compound was prepared by treatment of methyl 3-(*S*)-(*n*-butyl)-3-[(2-(*S*)-(*tert*-butoxycarbonyl)pyrrolidin-1-ylcarbonyl]-2-(*R*)-fluoropropionate (intermediate G-**4**, General Procedure G), with aqueous 50 % hydroxylamine followed by purification on preparative reverse-phase (C18) HPLC. ^{1}H NMR ($CDCl_3$): δ 5.32-5.13 (dd, $J_{H2,3}$ = 8.3 Hz & $J_{H,F}$ = 48 Hz, 1H), 4.54-4.51 (t, J = 4.1 Hz, 1H), 3.93-3.87 (m, 1H), 3.84-3.77 (m, 1H), 3.45-3.40 (m, 1H), 2.43-2.11 (m, 4H), 2.10-1.95 (m, 2H), 1.63 (s, 9H), 1.58-1.52 (m, 4H), 1.10 (t, J = 6.6 & 7.1 Hz, 3H). ES-MS: calcd. For $C_{17}H_{29}FN_2O_5$ (360.42); found: 361 [M+1].

Example 49

Synthesis of *N*-hydroxy-3-(*R*)-(*n*-butyl)-3-[2-(*S*)-(*tert*-butoxycarbonyl)-pyrrolidin-1-carbonyl]-2-oxopropionamide

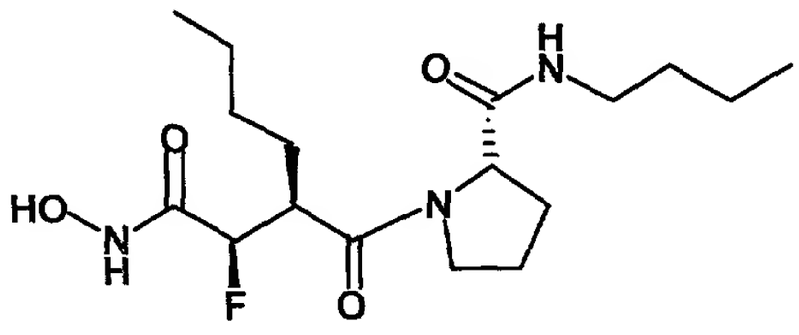


To a solution of methyl 3-(*R*)-(*n*-butyl)-3-[(2-(*S*)-(*tert*-butoxycarbonyl)-pyrrolidin-1-ylcarbonyl]-2-(*S*)-hydroxypropionate (intermediate **G-3** from General Procedure G, 2 mmol) in DCM (10 mL) at 0 °C was added pyridinium dichromate (2.2 mmol) and the solution stirred for 2h. The reaction was quenched with methanol,

then diluted with ethylacetate and washed with water, aqueous bicarbonate, and brine, then dried (Na_2SO_4) and puriifed on silica gel (ethylacetate/hexanes) to afford methyl 3-(*R*)-(*n*-butyl)-3-[(2-(*S*)-(*tert*-butoxycarbonyl)-pyrrolidin-1-ylcarbonyl]-2-oxo-propionate. To a solution of the 2-oxo intermediate (0.5 mmol) in dioxane (2 mL) was added aqueous 50 % hydroxylamine (1 mL) and the reaction stirred for 48 h. The crude reaction mixture was then purified by preparative reverse-phase (C18) HPLC to afford the title compound. ^{1}H NMR ($CDCl_3$): δ 4.41-4.39 (dd, J = 4.4 Hz), 4.29-4.24 (m, 1H), 3.99-3.96 (m, 1H), 3.70-3.67 (m, 1H), 2.29-1.97 (m, 4H), 1.79-1.77 (m, 2H), 1.43 (s, 9H), 1.37-1.35 (m, 4H), 0.91 (t, J = 6.7 & 7.1 Hz, 3H). ES-MS: calcd. For $C_{17}H_{28}N_2O_6$ (356.41); found: 357.4 [M+1].

Example 50

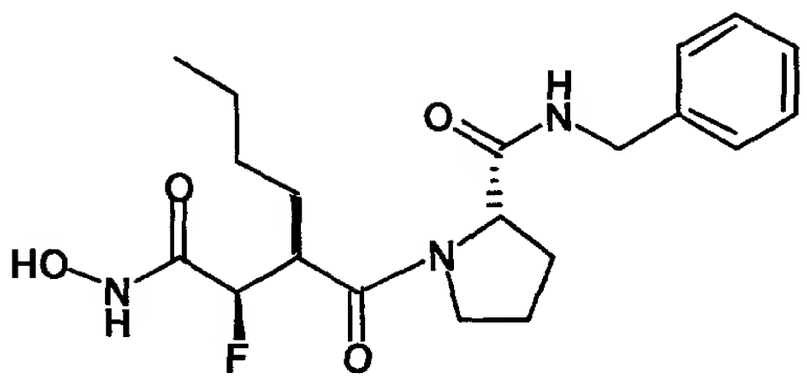
Synthesis of *N*-hydroxy-3-(*S*)-(*n*-butyl)-3-[2-(*S*)-(*n*-butylaminocarbonyl)-pyrrolidin-1-carbonyl]-2-(*R*)-fluoropropionamide



The title compound was prepared according to General Procedure G from *n*-butylamine. ^{1}H NMR ($CDCl_3$): δ 7.07 (t, J = 5.2 & 5.5Hz, 1H), 5.13 (dd, $J_{H2,3}$ = 8.5 Hz & $J_{H,F}$ = 47 Hz, 1H), 4.48-4.46 (dd, J = 4.9 Hz, 1H), 3.68-3.55 (m, 2H), 3.25-3.16 (m, 3H), 2.23-2.18 (m, 2H), 2.15-2.09 (m,4H), 2.06-1.80(m,4H), 1.52-1.43(m,4H), 1.32(t,J=7.5Hz,3H), 0.90(t,J=6.6&7.2Hz). ES-MS: cfalcd. For $C_{17}H_{30}FN_3O_4$ (359.44); found: 360.3 [M+1], 382.4 [M+Na].

Example 51

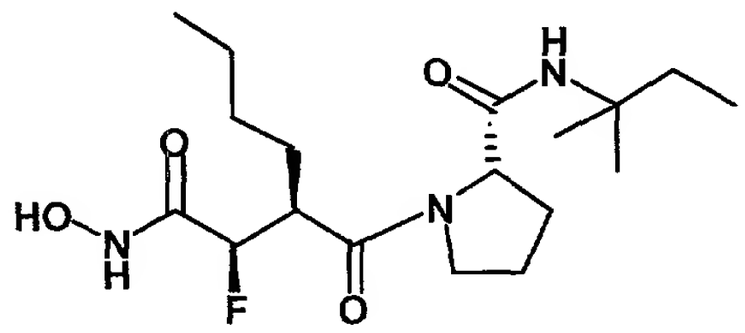
Synthesis of *N*-hydroxy-3-(*S*)-(*n*-butyl)-3-[2-(*S*)-(benzylaminocarbonyl)-pyrrolidin-1-carbonyl]-2-(*R*)-fluoropropionamide



The title compound was prepared according to General Procedure G from benzylamine. ^{1}H NMR ($CDCl_3$): δ 7.47-7.40 (m, 5H), 4.66-4.60 (dd, J = 5.1 Hz & 47 Hz, 1H), 4.58-4.45 (m, 1H), 3.97-3.76 (m, 4H), 3.35-3.28 (m, 1H), 2.31-1.94 (m, 6H), 1.61-1.45 (m, 4H), 1.07 (t, J = 6.6 Hz, 3H). ES-MS: calcd. For $C_{17}H_{28}FN_3O_4$ (393.45); found: 394.3 [M+1], 416.2 [M+Na].

Example 52

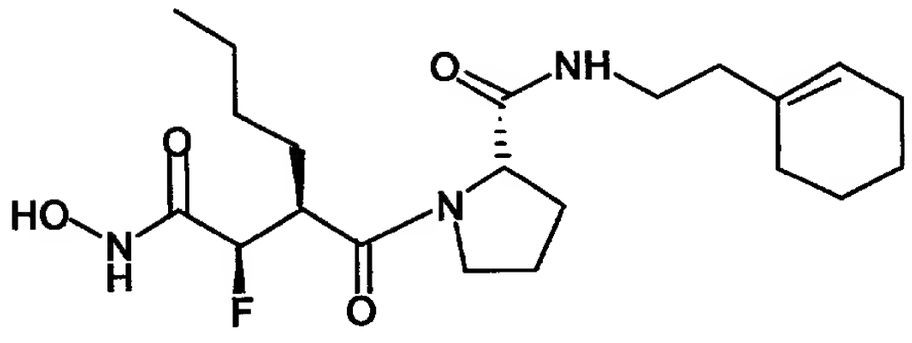
Synthesis of *N*-hydroxy-3-(*S*)-(*n*-butyl)-3-[2-(*S*)-(1,1-dimethylpropylamino-carbonyl)pyrrolidin-1-carbonyl]-2-(*R*)-fluoropropionamide



The title compound was prepared according to General Procedure G from 1,1-dimethylpropylamine. ^{1}H NMR ($CDCl_3$): δ 5.34-5.16 (dd, J = 7.9 & 8.3 Hz, $J_{H,F}$ = 47 Hz), 4.61 (d, J = 4.6 Hz), 3.80-3.78 (m, 2H), 3.40-3.35 (m, 1H), 2.39-1.84 (m, 8H), 1.53-1.44 (m, 10H), 1.09 (t, J = 6.8 Hz, 3H), 1.01 (t, J = 7.7 Hz, 3H). ES-MS: calcd. For $C_{18}H_{32}FN_3O_4$ (373.46); found: 374.4 [M+1], 396.2 [M+Na].

Example 53

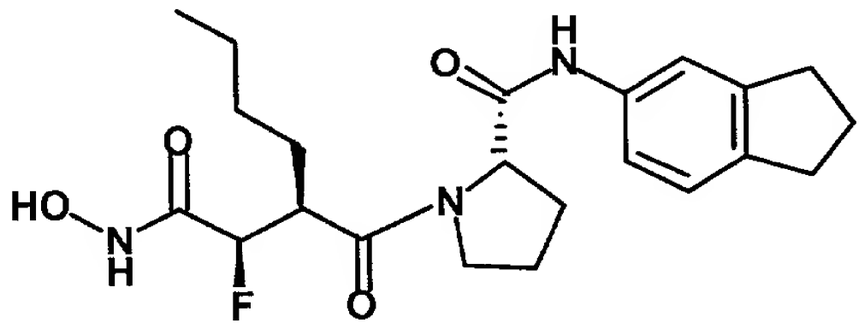
Synthesis of *N*-hydroxy-3-(*S*)-(*n*-butyl)-3-[2-(*S*)-(2-cyclohex-1-enylethylamino-carbonyl)pyrrolidin-1-carbonyl]-2-(*R*)-fluoropropionamide



The title compound was prepared according to General Procedure G from 2-(1-cyclohexenyl)ethylamine. ^{1}H NMR ($CDCl_3$): δ 7.11 (t, J = 4.6 & 5.2 Hz, 1H), 5.62 (bs, 1H), 5.32-5.13 (dd, J = 9.3 & 9.6 Hz, $J_{H,F}$ = 47 Hz, 1H), 4.64-4.63 (m, 1H), 3.81-3.73 (m, 2H), 3.59-3.52 (m, 1H), 3.50-3.37 (m, 3H), 2.31-2.16 (m, 9H), 2.10-1.99 (m, 2H), 1.79-1.52 (m, 9H), 1.09 (t, J = 6.5 & 5.5Hz). ES-MS: calcd. For $C_{21}H_{34}FN_3O_4$ (411.51); found: 412.4[M+1], 434.5 [M+Na].

Example 54

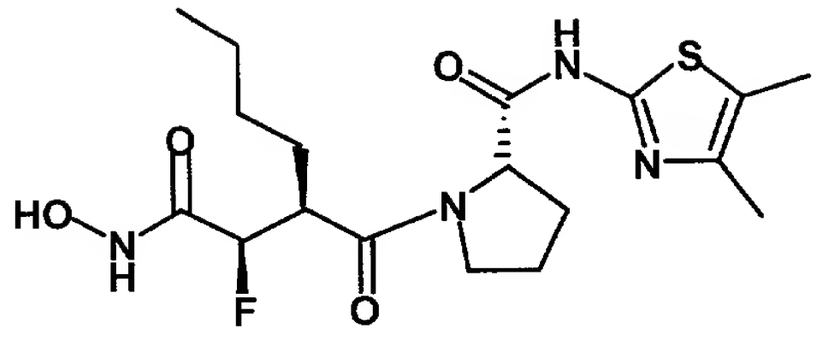
Synthesis of *N*-hydroxy-3-(*S*)-(*n*-butyl)-3-[2-(*S*)-(indan-5-ylamino-carbonyl)pyrrolidin-1-carbonyl]-2-(*R*)-fluoropropionamide



The title compound was prepared according to General Procedure G from 5-aminoindan. ^{1}H NMR ($CDCl_3$): δ 7.52 (s,1H), 7.35 (d, J = 8 Hz, 1H), 7.21 (d, J = 8 Hz, 1H), 5.34-5.15 (dd, J =8.2 & 8.5 Hz, $J_{H,F}$ = 47 Hz, 1H), 4.86-4.84 (m, 1H), 3.80-3.78 (m, 2H), 3.36-3.31 (m, 1H), 3.06-2.96 (m, 4H), 2.41-1.97 (m, 8H), 1.58-1.48 (m, 4H), 1.04 (t, J = 6.6 & 7.2 Hz, 3H). ES-MS: calcd. For $C_{22}H_{30}FN_3O_4$ (419.49); found: 420.3 [M+1].

Example 55

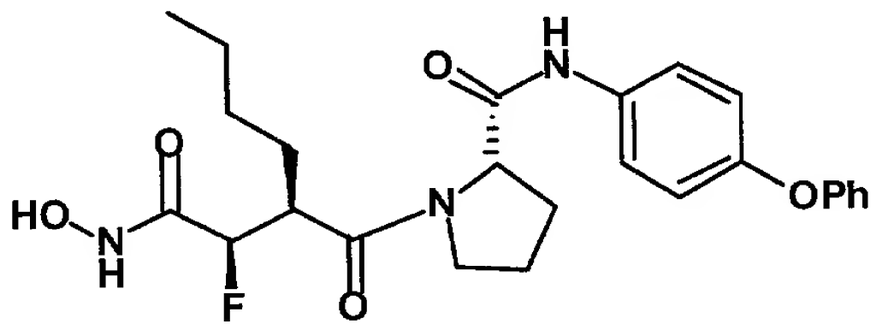
Synthesis of *N*-hydroxy-3-(*S*)-(*n*-butyl)-3-[2-(*S*)-(4,5-dimethylthiazol-2-ylamino-carbonyl)pyrrolidin-1-carbonyl]-2-(*R*)-fluoropropionamide



The title compound was prepared according to General Procedure G from 2-amino-4,5-dimethylthiazole. ^{1}H NMR ($CDCl_3$): δ 5.32-5.13 (dd, J = 8.3 & 7.9 Hz, $J_{H,F}$ = 47 Hz, 1H), 4.83-4.80 (m, 1H), 3.97-3.85 (m, 2H), 3.40-3.38 (m, 1H), 2.51 (s, 3H), 2.50 (s, 3H), 2.33-2.21 (m, 4H), 2.18-1.95 (m, 2H), 1.59-1.49 (m, 4H), 1.07 (t, J = 6.6 & 7.2 Hz, 3H). ES-MS: calcd. For $C_{18}H_{27}FN_4O_4S$ (414.50); found: 415.4 [M+1], 437.3 [M+Na].

Example 56

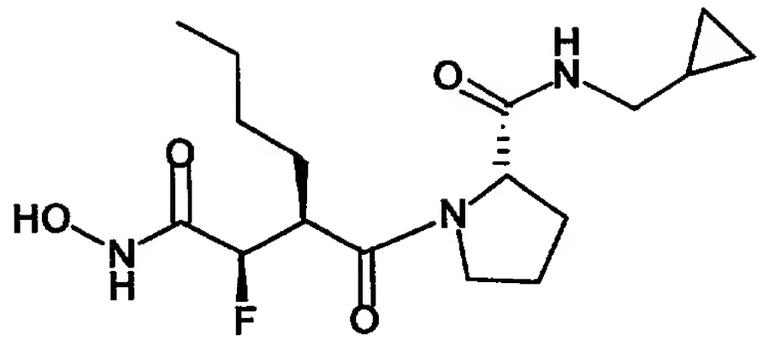
Synthesis of *N*-hydroxy-3-(*S*)-(*n*-butyl)-3-[2-(*S*)-(4-phenoxyphenyl)amino-carbonyl)pyrrolidin-1-carbonyl]-2-(*R*)-fluoropropionamide



The title compound was prepared according to General Procedure G from 4-phenoxyaniline. ^{1}H NMR ($CDCl_3$): δ 7.69-7.16 (m, 2H), 7.53-7.46 (m, 2H), 7.29-7.24 (m, 1H), 7.18-7.06 (m, 4H), 5.37-5.20 (dd, J = 7.8 Hz, $J_{H,F}$ = 47 Hz, 1H), 4.90-4.85 (m, 1H), 3.92-3.82 (m, 2H), 3.33-3.37 (m, 1H), 2.47-2.36 (m, 2H), 2.30-2.00 (m, 4H), 1.50-1.13 (m, 4H), 1.02 (t, J = 6.6 & 6.9 Hz, 3H). ES-MS: calcd. For $C_{25}H_{30}FN_3O_5$ (471.52); found: 472.4 [M+1].

Example 57

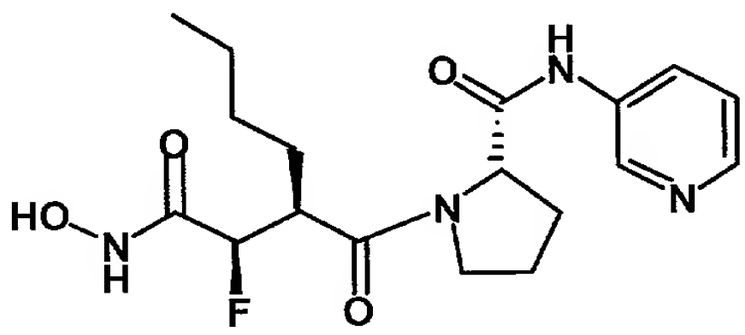
Synthesis of *N*-hydroxy-3-(*S*)-(*n*-butyl)-3-[2-(*S*)-(cyclopropylmethylamino-carbonyl)pyrrolidin-1-carbonyl]-2-(*R*)-fluoropropionamide



The title compound was prepared according to General Procedure G from (aminomethyl)cyclopropane. ^{1}H NMR ($CDCl_3$): δ 6.90 (t, J = 5.2 Hz, 1H), 4.99-4.82 (dd, J = 6.4 & 8 Hz, $J_{H,F}$ = 49.8 & 48.6 Hz,1H), 4.34-4.32 (m, 1H), 3.56-3.47 (m, 2H), 3.09-2.85 (m, 3H), 2.09-1.83 (m, 4H), 1.67-1.64 (m, 2H), 1.30-1.11 (m, 5H), 0.72 (t, J = 6.9 & 7.1 Hz, 3H), 0.33-0.29 (dd, J = 5.3 Hz, 2H), 0.05-0.00 (dd, J = 4.6 Hz, 2H). ES-MS: calcd. For $C_{17}H_{28}FN_3O_4$ (357.42); found: 358.4 [M+1].

Example 58

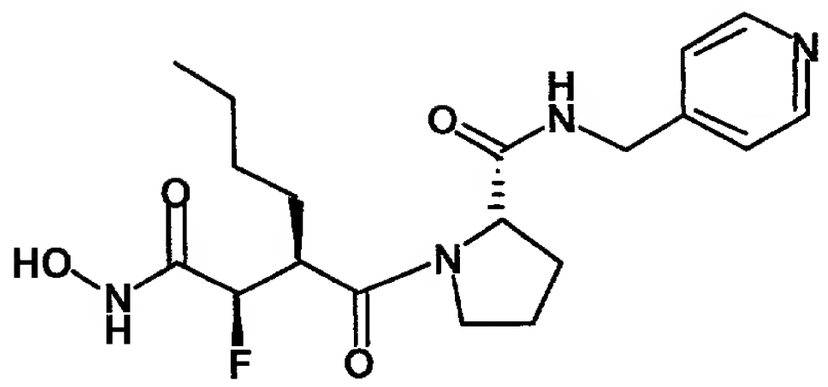
Synthesis of *N*-hydroxy-3-(*S*)-(*n*-butyl)-3-[2-(*S*)-(pyridin-3-yl)amino-carbonyl)pyrrolidin-1-carbonyl]-2-(*R*)-fluoropropionamide



The title compound was prepared according to General Procedure G from 3-aminopyridine. ^{1}H NMR (DMSO-D6): δ 9.15 (s, 1H), 8.62 (d, J = 4.2 Hz, 1H), 8.42 (d, J = 8.2 Hz, 1H), 7.88-7.83 (dd, J = 5.3 & 4.9 Hz, 1H), 5.09-4.91 (dd, J = 8 Hz, $J_{H,F}$ = 48.6 Hz, 1H), 4.60-4.56 (dd, J = 4.8 Hz, 1H), 3.92-3.89 (m, 1H), 3.87-3.79 (m, 1H), 3.42-3.35 (m, 1H), 2.37-2.04 (m, 4H), 1.81-1.51 (m, 2H), 1.50-1.39 (m, 4H), 1.04 (t, J = 6.9 & 7.2 Hz, 3H). ES-MS: calcd. For $C_{18}H_{25}FN_4O_4$ (380.41); found: 381.3 [M+1].

Example 59

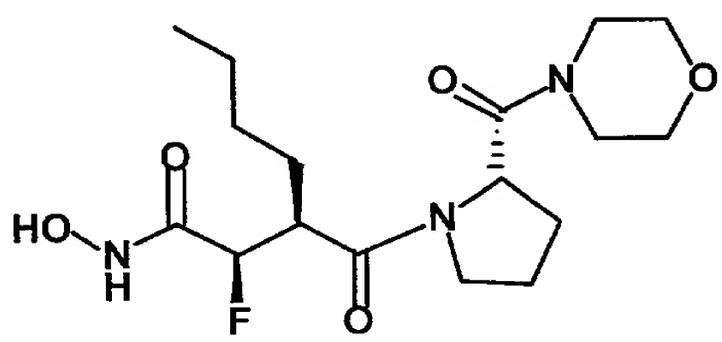
Synthesis of *N*-hydroxy-3-(*S*)-(*n*-butyl)-3-[2-(*S*)-((pyridin-4-ylmethyl)amino-carbonyl)pyrrolidin-1-carbonyl]-2-(*R*)-fluoropropionamide



The title compound was prepared according to General Procedure G from 4-(aminomethyl)pyridine. ^{1}H NMR (DMSO-D6): δ 8.94-8.86 (m, 3H), 7.94-7.93 (m, 1H), 5.14-4.95 (dd, J = 7.7 Hz, $J_{H,F}$ = 48.4 Hz, 1H), 4.68-4.67 (m, 1H), 4.51-4.47 (m, 1H), 3.95-3.75 (m, 3H), 3.38-3.35 (m, 1H), 2.33-2.01 (m, 4H), 1.99-1.79 (m, 2H), 1.41-1.38 (m, 4H), 0.92 (t, J = 6.6 & 7.1 Hz, 3H). ES-MS: calcd. For $C_{19}H_{27}FN_4O_4$ (394.44); found: 395.4 [M+1].

Example 60

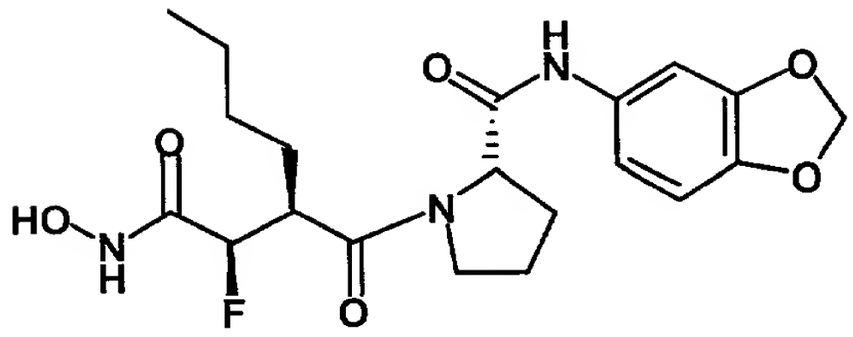
Synthesis of *N*-hydroxy-3-(*S*)-(*n*-butyl)-3-[2-(*S*)-(morpholin-4-ylcarbonyl)pyrrolidin-1-carbonyl]-2-(*R*)-fluoropropionamide



The title compound was prepared according to General Procedure G from morpholine. ^{1}H NMR ($CDCl_3$): δ 5.30-5.11 (dd, J = 8.2 Hz, $J_{H.F}$ = 47.6 Hz, 1H), 5.06-5.04 (t, J = 3.6 & 4.4 Hz, 1H), 3.92-3.67 (m, 10H), 3.44-3.42 (m, 1H), 2.40-1.98 (m, 6H), 1.74-1.52 (m, 4H), 1.10 (t, J = 6.8 & 7.4 Hz, 3H). ES-MS: calcd. For $C_{17}H_{28}FN_3O_5$ (373.42); found: 374.3[M+1].

Example 61

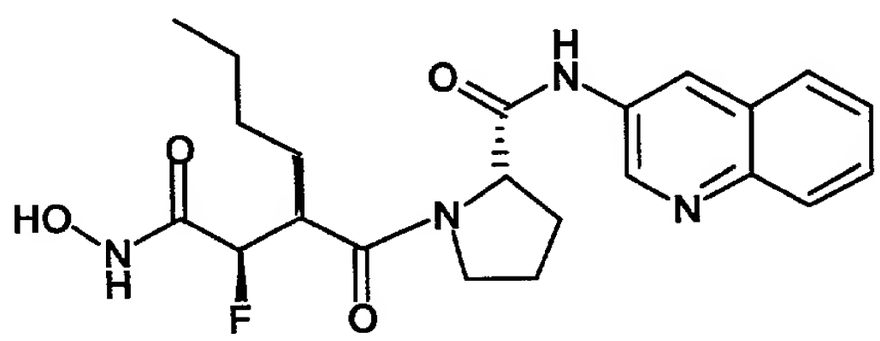
Synthesis of *N*-hydroxy-3-(*S*)-(*n*-butyl)-3-[2-(*S*)-(3,4-methylenedioxyphenyl-aminocarbonyl)pyrrolidin-1-carbonyl]-2-(*R*)-fluoropropionamide



The title compound was prepared according to General Procedure G from 3,4-(methylenedioxy)aniline. ^{1}H NMR ($CDCl_3$): δ 7.47 (s, 1H), 7.34 (d, J = 2Hz, 1H), 6.99-6.95 (dd, J = 2Hz, 1H), 6.80 (d, J = 8.5 Hz, 1H), 6.08 (s, 2H), 5.36-5.17 (dd, J = 8.5 & 8.8 Hz, $J_{H,F}$ = 47 Hz, 1H), 4.82-4.81 (dd, J = 4.4 Hz, 1H), 3.84-3.80 (m, 2H), 3.38-3.33 (m, 1H), 2.40-1.97 (m, 6H), 1.57-1.52 (m, 4H), 1.059 (t, J = 6.9 & 7.1 Hz, 3H). ES-MS: calcd. For $C_{20}H_{26}FN_3O_6$ (423.44); found: 424.3 [M+1].

Example 62

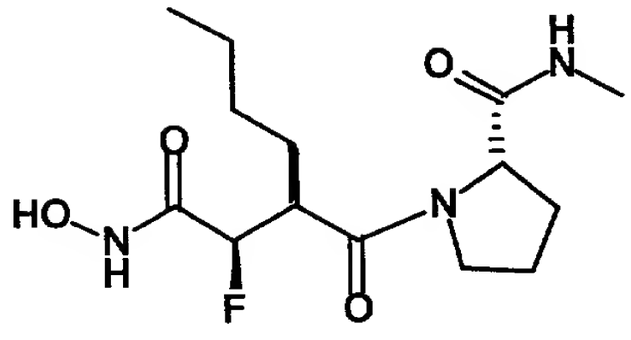
Synthesis of *N*-hydroxy-3-(*S*)-(*n*-butyl)-3-[2-(*S*)-(quinolin-3-ylamino-carbonyl)pyrrolidin-1-carbonyl]-2-(*R*)-fluoropropionamide



The title compound was prepared according to General Procedure G from 3-aminoquinoline. ^{1}H NMR ($CDCl_3$): δ 9.32 (s,1H), 8.31 (d, J = 8.8 Hz, 1H), 8.03-7.81 (m, 3H), 7.48-7.46 (m, 2H), 5.35-5.17 (dd, J = 7.7 & 8 Hz, $J_{H,F}$ = 47 Hz, 1H), 4.89-4.85 (m, 1H), 3.90-3.85 (m, 2H), 3.45-3.37 (m, 1H), 2.41-2.02(m, 5H), 1.67-1.52 (m, 5H), 1.10 (t, J = 6.9 & 5.7 Hz, 3H). ES-MS: calcd. For $C_{22}H_{27}FN_4O_4$ (430.47); found: 431.3 [M+1].

Example 63

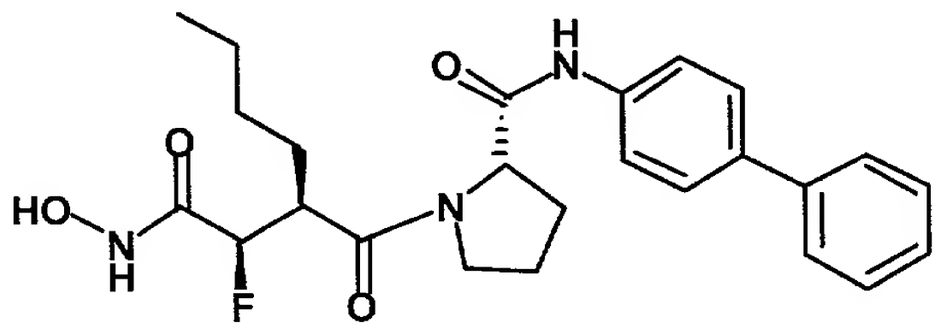
Synthesis of *N*-hydroxy-3-(*S*)-(*n*-butyl)-3-[2-(*S*)-(methylaminocarbonyl)-pyrrolidin-1-carbonyl]-2-(*R*)-fluoropropionamide



The title compound was prepared according to General Procedure G from methylamine. ^{1}H NMR ($CDCl_3$): δ 7.30 (d, J = 5.6 Hz, 1H), 5.30-5.12 (dd, J = 7.9 & 8.8 Hz, $J_{H,F}$ = 47 Hz, 1H), 3.84-3.82 (m, 2H), 3.41-3.39 (m, 1H), 2.95 (s, 3H), 2.32-1.99 (m, 6H), 1.63-1.51 (m, 4H), 1.09 (t, J = 6.4 & 4.9 Hz, 3H). ES-MS: calcd. For $C_{14}H_{24}FN_3O_4$ (317.36); found 318.3 [M+1].

Example 64

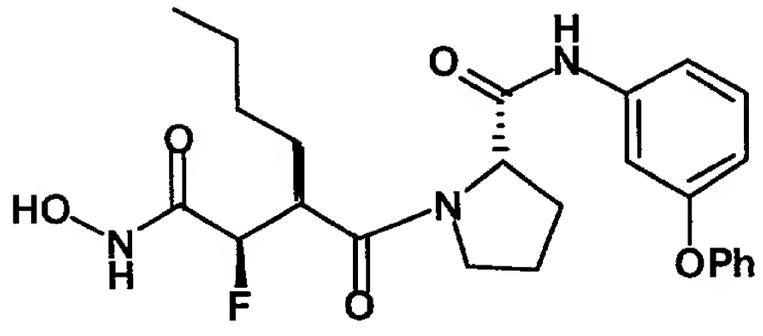
Synthesis of *N*-hydroxy-3-(*S*)-(*n*-butyl)-3-[2-(*S*)-((4-biphenyl)aminocarbonyl)-pyrrolidin-1-carbonyl]-2-(*R*)-fluoropropionamide



The title compound was prepared according to General Procedure G from 4-phenylaniline. ^{1}H NMR ($CDCl_3$): δ 7.75-7.46 (m, 10H), 5.39-5.21 (dd, J = 8.8 Hz, $J_{H,F}$ = 47 Hz, 1H), 4.91-4.89 (m, 1H), 3.85-3.83 (m, 2H), 3.41-3.36 (m, 1H), 2.45-2.02 (m, 6H), 1.63-1.50 (m, 4H), 1.06 (t, J = 6.6 & 7.4 Hz, 3H). ES-MS: calcd. For $C_{25}H_{30}FN_3O_4$ (455.52); found 456.3 [M+1].

Example 65

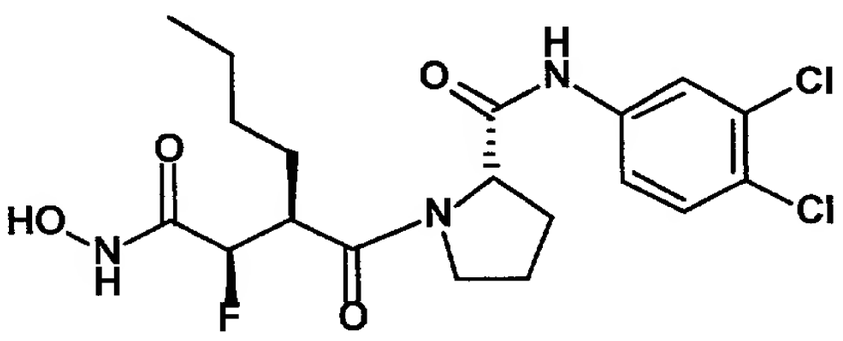
Synthesis of *N*-hydroxy-3-(*S*)-(*n*-butyl)-3-[(2-(*S*)-((3-phenoxyphenyl)aminocarbonyl)-pyrrolidin-1-carbonyl]-2-(*R*)-fluoropropionamide



The title compound was prepared according to General Procedure G from 3-phenoxyaniline. ^{1}H NMR (CDCl3): δ 7.53-7.46 (m, 4H), 7.35-7.25 (m, 3H), 7.18-7.14 (m, 2H), 6.85-6.18 (m, 1H), 5.35-5.16 (dd, J = 8.8 Hz, $J_{H,F}$ = 47 Hz, 1H), 4.84-4.82 (m, 1H), 3.81-3.78 (m, 2H), 3.36-3.31 (m, 1H), 2.41-1.97 (m, 6H), 1.53-1.46 (m, 4H), 1.02 (t, J = 6.6 & 7.1 Hz, 3H). ES-MS: calcd. For $C_{25}H_{30}FN_3O_5$ (471.52); found 472.4 [M+1].

Example 66

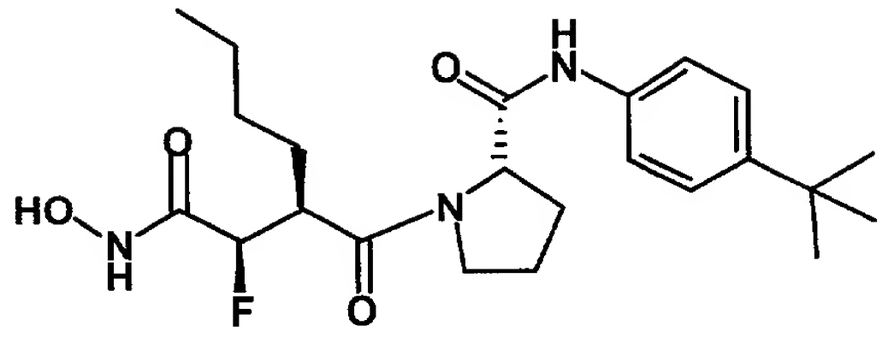
Synthesis of *N*-hydroxy-3-(*S*)-(*n*-butyl)-3-[2-(*S*)-((3,4-dichlorophenyl)amino-carbonyl)pyrrolidin-1-carbonyl]-2-(*R*)-fluoropropionamide



The title compound was prepared according to General Procedure G from 3,4-dichloroaniline. ^{1}H NMR ($CDCl_3$): δ 7.78 (s, 1H), 7.47-7.32 (m, 2H), 5.35-5.16 (dd, J = 8.8 Hz, $J_{H,F}$ = 47 Hz, 1H) 4.82-4.80 (m, 1H), 3.85-3.79 (m, 2H), 3.36-3.31 (m, 1H), 2.35-2.03 (m, 6H), 1.67-1.54 (m,4H), 1.10 (t, J = 6.6 & 6.8 Hz, 3H). ES-MS: calcd. For $C_{19}H_{24}Cl_2FN_3O_4$ (444.11); found: 448.2 [M+1].

Example 67

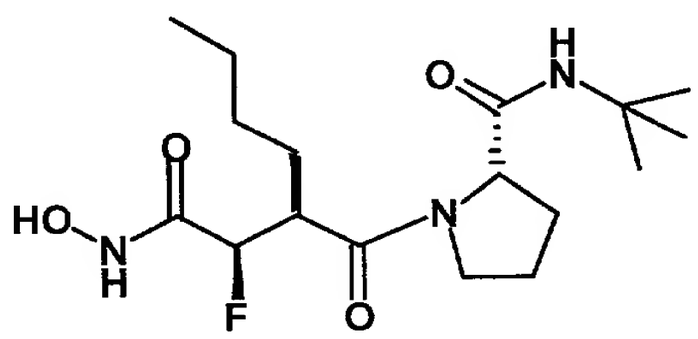
Synthesis of *N*-hydroxy-3-(*S*)-(*n*-butyl)-3-[2-(*S*)-((4-*tert*-butylphenyl)amino-carbonyl)pyrrolidin-1-carbonyl]-2-(*R*)-fluoropropionamide



The title compound was prepared according to General Procedure G from 4-*tert*-butylaniline. ^{1}H NMR ($CDCl_3$): δ 7.67(m,2H), 7.57-7.45 (m, 3H), 5.35-5.16 (dd, J = 8.2 & 8.5 Hz, $J_{H,F}$ = 47 Hz, 1H), 4.85 (d, J = 4.4 Hz, 1H), 3.83-3.80 (m, 2H), 3.39-3.34 (m, 1H), 2.43-2.00 (m,6H), 1.57-1.45 (m, 13H), 1.023 (t, J = 6.6 & 7.1 Hz, 3H). ES-MS: calcd. For $C_{23}H_{34}FN_3O_4$ (435.53); found: 436.4 [M+1].

Example 68

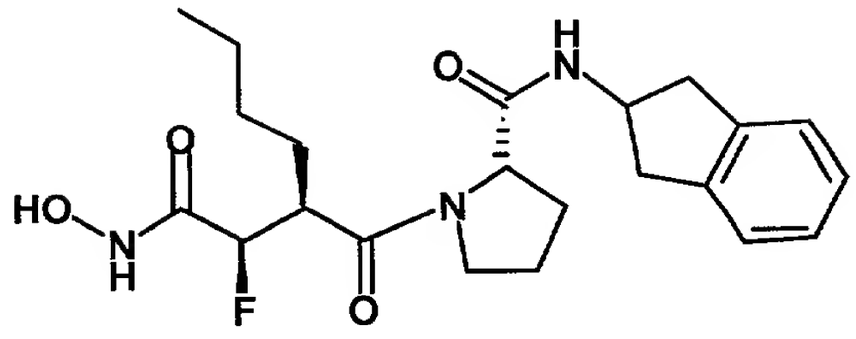
Synthesis of *N*-hydroxy-3-(*S*)-(*n*-butyl)-3-[2-(*S*)-(*tert*-butylaminocarbonyl)-pyrrolidin-1-carbonyl]-2-(*R*)-fluoropropionamide



The title compound was prepared according to General Procedure G from *tert*-butylamine. ^{1}H NMR ($CDCl_3$): δ 5.33-5.14 (dd, J = 8 Hz, $J_{H,F}$ = 48 Hz, 1H), 4.58 (d, J = 4.7 Hz, 1H), 3.81-3.79 (m, 2H), 3.42-3.39 (m, 1H), 2.40-1.98 (m, 10H), 1.55-1.49 (m, 13H), 1.11 (t, J = 5.8 & 6.6 Hz, 3H). ES-MS: calcd. For $C_{17}H_{30}FN_3O_4$ (359.44); found: 360.3 [M+1].

Example 69

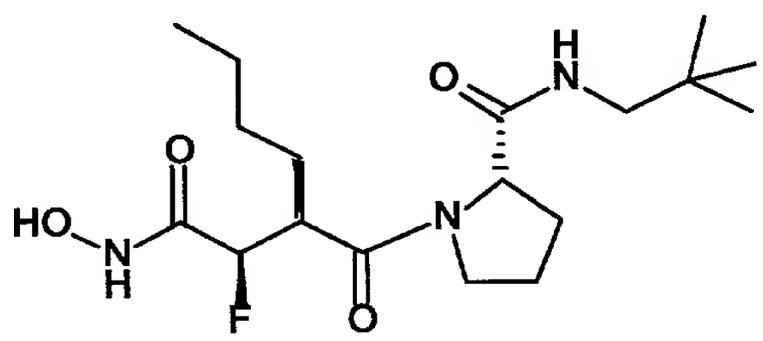
Synthesis of *N*-hydroxy-3-(*S*)-(*n*-butyl)-3-[2-(*S*)-((indan-2-yl)amino-carbonyl)pyrrolidin-1-carbonyl]-2-(*R*)-fluoropropionamide



The title compound was prepared according to General Procedure G from 2-aminoindan. ^{1}H NMR ($CDCl_3$): δ 7.48-7.33 (m, 4H), 5.25-5.07 (dd, J = 8.5 Hz, $J_{H,F}$ = 47.5 Hz, 1H), 4.86-4.80 (m,1H), 4.57-4.55 (m,1H), 3.78-3.76 (m,2H), 3.51-3.42 (m,2H), 3.35-3.30 (m,1H), 3.01-2.92 (m,2H), 2.37-2.27 (m,2H), 2.17-1.92 (m,2H), 1.52-1.42 (m,4H), 1.08 (t, J = 6.8 Hz, 3H). ES-MS: calcd. For $C_{22}H_{30}FN_3O_4$ (419.49); found: 420.6 [M+1].

Example 70

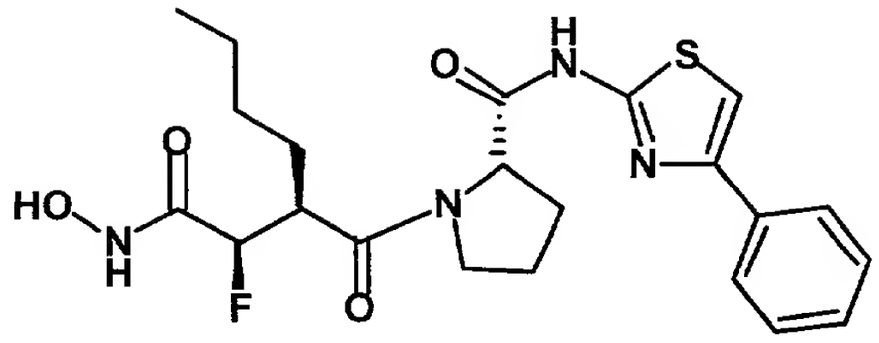
Synthesis of *N*-hydroxy-3-(*S*)-(*n*-butyl)-3-[2-(*S*)-((2,2-dimethylpropyl)amino-carbonyl)pyrrolidin-1-carbonyl]-2-(*R*)-fluoropropionamide



The title compound was prepared according to General Procedure G from 2,2-dimethylpropylamine. ^{1}H NMR ($CDCl_3$): δ 7.28 (t, J = 6 Hz, 1H), 5.36-5.18 (dd, J = 8.4 Hz, $J_{H,F}$ = 47.5 Hz, 1H), 4.75 (d, J = 5.2 Hz, 1H), 3.85-3.77 (m, 2H), 3.40-3.35 (m, 1H), 3.29-3.19 (m, 2H), 2.50-2.27 (m, 2H), 2.17-2.13 (m, 2H), 2.09-1.98 (m,2H), 1.53-1.51 (m,4H), 1.08 (bs,3H). $C_{18}H_{32}FN_3O_4$ (373.24); found: 374.4 [M+1].

Example 71

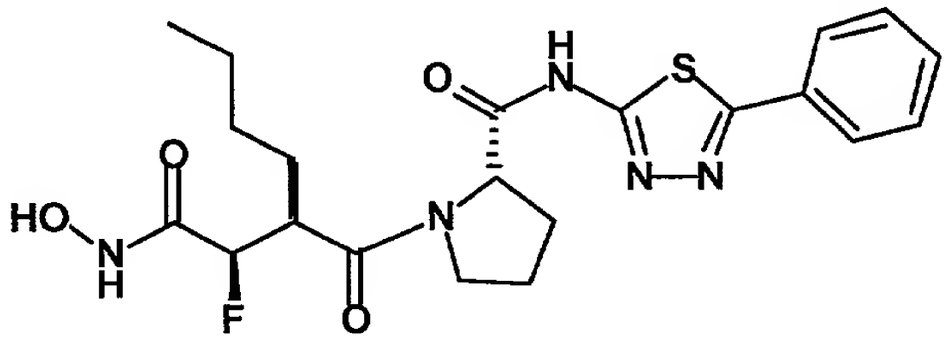
Synthesis of *N*-hydroxy-3-(*S*)-(*n*-butyl)-3-[2-(*S*)-((4-phenylthiazol-2-yl)amino-carbonyl)pyrrolidin-1-carbonyl]-2-(*R*)-fluoropropionamide



The title compound was prepared according to General Procedure G from 2-amino-4-phenylthiazole. ^{1}H NMR ($CDCl_3$): δ 7.92–7.90 (m, 2H), 7.71 (m, 3H), 7.46 (s,1H), 7.28 (s,1H), 5.37 – 5.18 (dd, J = 8.5 & 8.2 Hz, $J_{H,F}$ = 47 Hz, 1H), 4.95–4.93 (m,1H), 3.99–3.95 (m,2H), 3.43–3.38 (m,1H), 2.54–2.26 (m,4H), 2.21–1.96 (m,2H), 1.62–1.50 (m,4H), 1.08 (t, J = 6.9 & 7.1 Hz, 3H). ES-MS: calcd. For $C_{22}H_{27}FN_4O_4S$ (462.54); found: 463.4 [M+1].

Example 72

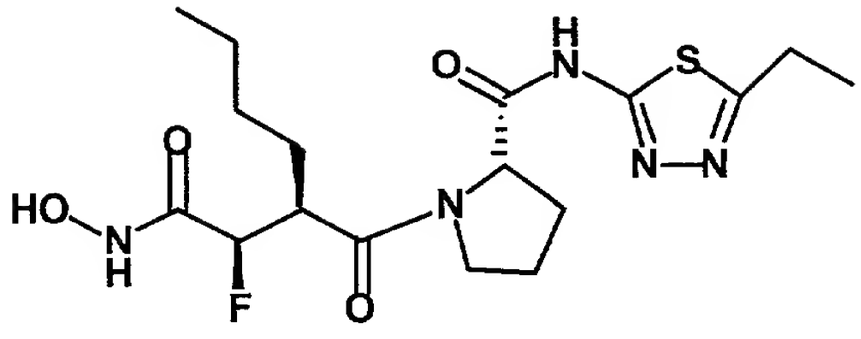
Synthesis of *N*-hydroxy-3-(*S*)-(*n*-butyl)-3-[2-(*S*)-((5-phenylthiadiazol-2-yl)amino-carbonyl)pyrrolidin-1-carbonyl]-2-(*R*)-fluoropropionamide



The title compound was prepared according to General Procedure G from 2-amino-5-phenylthiadiazole. ^{1}H NMR ($CDCl_3$): δ 8.08–8.05 (m,2H), 7.68–7.48 (m, 3H), 5.45–5.26 (dd, J = 9.2 Hz, $J_{H,F}$ = 47 Hz, 1H), 4.99–4.97 (m,1H), 3.96–3.94 (m,2H), 3.38–3.36 (m,1H), 2.50–1.98 (m, 6H), 1.61–1.51 (m,4H), 1.09 (t, J = 6.9 Hz, 3H). ES-MS: calcd. For $C_{21}H_{26}FN_5O_4S$ (463.53); found: 464.2 [M+1].

Example 73

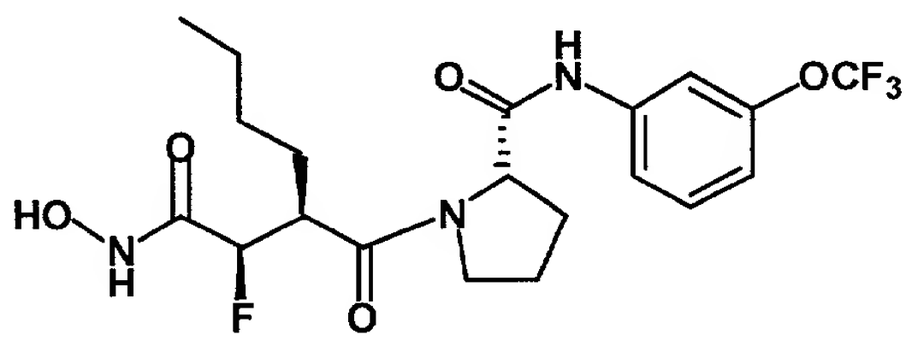
Synthesis of *N*-hydroxy-3-(*S*)-(*n*-butyl)-3-[2-(*S*)-((5-ethylthiadiazol-2-yl)amino-carbonyl)pyrrolidin-1-carbonyl]-2-(*R*)-fluoropropionamide



The title compound was prepared according to General Procedure G from 2-amino-5-ethylthiadiazole. ^{1}H NMR ($CDCl_3$): δ 5.43–5.24 (dd, J = 9.6 Hz, $J_{H,F}$ = 47.5 Hz, 1H), 5.00–4.98 (m, 1H), 3.97–3.88 (m, 1H), 3.38–3.36 (m,2H), 3.27–3.20 (m, 2H), 2.47–2.21 (m, 4H), 2.19–1.97 (m,2H), 1.58 (t, J = 7.7 Hz, 3H), 1.58–1.49 (m, 4H), 1.09 (t, J = 6.8 & 7.2 Hz, 3H). ES-MS: calcd. For $C_{17}H_{26}FN_5O_4S$ (415.48); found: 416.2 [M+1].

Example 74

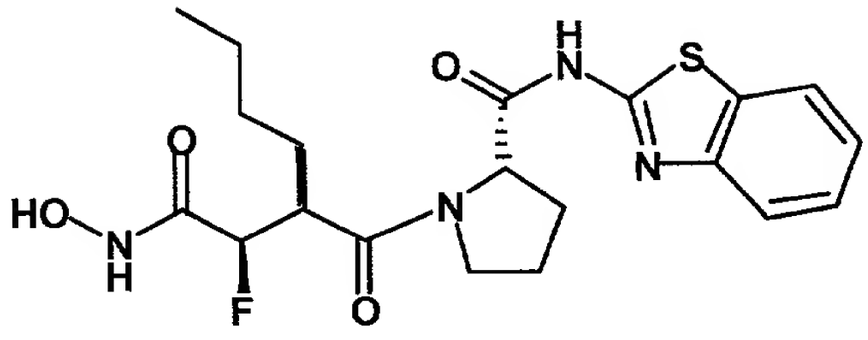
Synthesis of *N*-hydroxy-3-(*S*)-(*n*-butyl)-3-[2-(*S*)-((3-trifluoromethoxyphenyl)amino-carbonyl)pyrrolidin-1-carbonyl]-2-(*R*)-fluoropropionamide



The title compound was prepared according to General Procedure G from 3-(trifluoromethoxy)aniline. ^{1}H NMR ($CDCl_3$): δ 7.71 (s,1H), 7.48–7.41 (m, 2H), 7.29 (t, J = 8.2 Hz, 1H), 6.98 (d, J = 7.9 Hz, 1H), 5.39–5.21 (dd, J = 9.3 & 8.8 Hz, 1H), 4.88–4.86 (m, 1H), 3.85–3.82 (m, 2H), 3.39–3.37 (m,1H), 2.41–2.04 (m, 6H), 1.61–1.53 (m, 4H), 1.06 (t, J = 6.9 Hz, 3H). ES-MS: calcd. For $C_{20}H_{25}F_4N_3O_5$ (463.42); found: 454.2 [M + 1].

Example 75

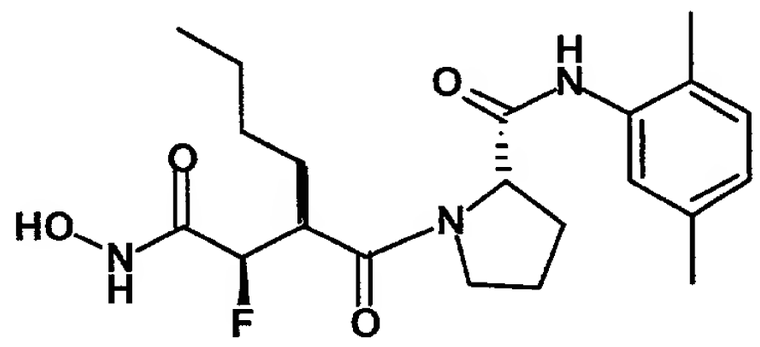
Synthesis of *N*-hydroxy-3-(*S*)-(*n*-butyl)-3-[2-(*S*)-((benzthiazol-2-yl)amino-carbonyl)pyrrolidin-1-carbonyl]-2-(*R*)-fluoropropionamide



The title compound was prepared according to General Procedure G from 2-aminobenzothiazole. ^{1}H NMR ($CDCl_3$): δ 7.99–7.92 (dd, J = 7.5 & 8.2 Hz, 2H), 7.70–7.64 (dd, J = 8 & 7.6 Hz, 1H), 7.56 (t, J = 7.9 & 8.5 Hz, 1H), 5.43–5.24 (dd, J = 8.2 & 8.5 Hz, $J_{H,F}$ = 47 Hz, 1H), 5.04 – 5.01 (m, 1H), 4.00–3.97 (m, 2H), 3.47–3.42 (m, 1H), 2.57–2.21 (m, 4H), 2.00 – 1.97 (m, 2H), 1.64–1.52 (m, 4H), 1.09 (t, J = 6.8 & 7.2 Hz, 3H). ES-MS: calcd. For $C_{20}H_{25}F\,N_4O_4S$ (436.50); found: 437.3 [M+1].

Example 76

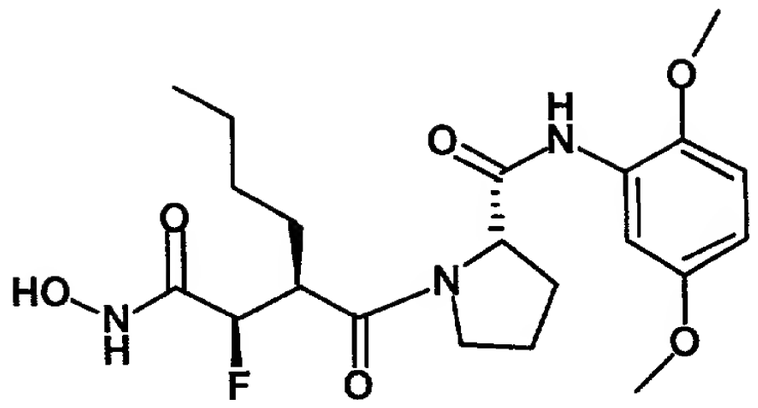
Synthesis of *N*-hydroxy-3-(*S*)-(*n*-butyl)-3-[2-(*S*)-((2,5-dimethylphenyl)amino-carbonyl)pyrrolidin-1-carbonyl]-2-(*R*)-fluoropropionamide



The title compound was prepared according to General Procedure G from 2,5-dimethylaniline. ^{1}H NMR ($CDCl_3$): δ 7.81 (s,1H), 7.22 (d, J = 7.7 Hz, 1H), 7.05 (d, J = 7.9 Hz, 1H), 5.42–5.23 (dd, J = 8.5 Hz, $J_{H,F}$ = 47 Hz, 1H), 4.99–4.97 (m, 1H), 3.83–3.79 (m, 2H), 3.40–3.35 (m, 1H), 2.66–2.63 (m, 2H), 2.47 (s, 3H), 2.38 (s, 3H), 2.24–2.19 (m,2H), 2.18–1.99 (m, 2H), 1.64–1.46 (m, 4H), 0.99 (t, J = 6.6 & 6.9 Hz, 3H). ES-MS: calcd. For $C_{21}H_{30}F\,N_3O_4$ (407.48); found: 408.3 [M+1].

Example 77

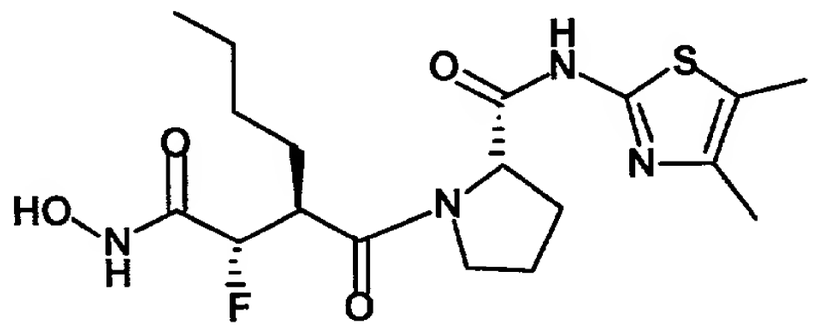
Synthesis of *N*-hydroxy-3-(*S*)-(*n*-butyl)-3-[2-(*S*)-((2,5-dimethoxyphenyl)amino-carbonyl)pyrrolidin-1-carbonyl]-2-(*R*)-fluoropropionamide



The title compound was prepared according to General Procedure G from 2,5-dimethoxyaniline. ^{1}H NMR ($CDCl_3$): δ 8.22 (d, J = 3 Hz, 1H), 6.96 (d, J = 8.8 Hz. 1H), 6.79 – 6.75 (dd, J = 3 Hz, 1H), 5.41–5.22 (dd, J = 8 Hz; $J_{H,F}$ = 47 Hz, 1H), 4.92–4.90 (m, 1H), 4.00 (s, 3H), 3.96 (s, 3H), 3.95–3.85 (m, 2H), 3.45–3.39 (m, 1H), 2.56–2.23 (m, 4H), 2.02–1.99 (m, 2H), 1.64–1.49 (m, 4H), 1.00 (t, J = 6.3 & 7.1 Hz, 3H). ES-MS: calcd. For $C_{21}H_{30}F\,N_3O_6$ (439.48); found: 440.4 [M + 1].

Example 78

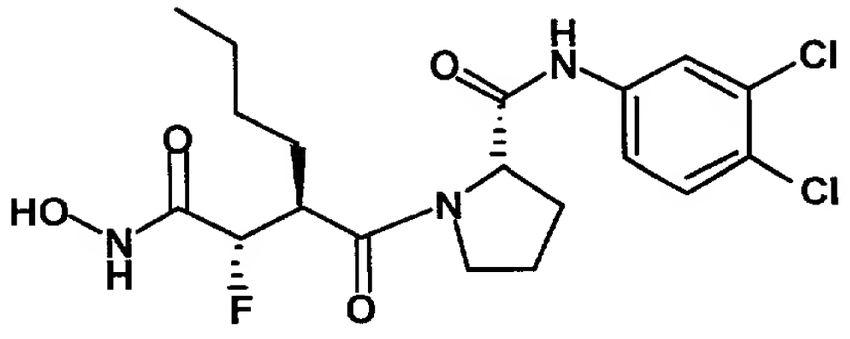
Synthesis of *N*-hydroxy-3-(*S*)-(*n*-butyl)-3-[2-(*S*)-((4,5-dimethylthiazol-2-yl)amino-carbonyl)pyrrolidin-1-carbonyl]-2-(*S*)-fluoropropionamide



The title compound was prepared according to General Procedure H from 2-amino-4,5-dimethylthiazole. ^{1}H NMR ($CDCl_3$): δ 5.32–5.14 (dd, J = 5.7 Hz, $J_{H,F}$ = 47 Hz, 1H), 4.85 – 4.81 (dd, J = 6 & 5.3 Hz, 1H), 4.03–3.99 (m, 2H), 3.53–3.43 (m, 1H), 2.52 (s, 3H), 2.50 (s, 3H), 2.36–2.22 (m, 4H), 2.19–1.79 (m, 2H), 1.60–1.50 (m, 4H), 1.08 (t, J = 6.6 & 6.9 Hz, 3H). ES-MS: calcd. For $C_{18}H_{27}F\,N_4O_4S$ (414.50); found: 415.4 [M + 1].

Example 79

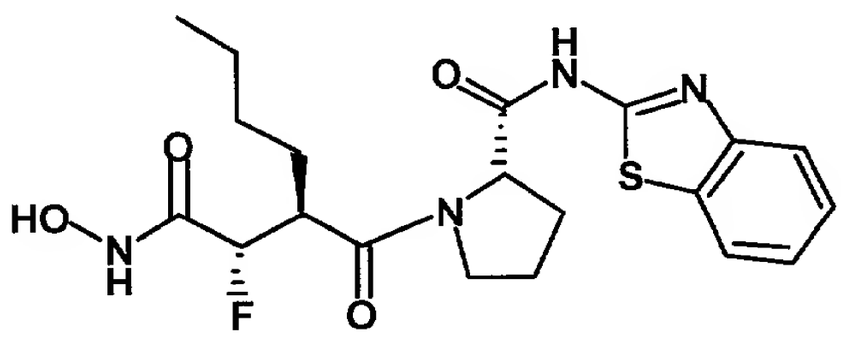
Synthesis of *N*-hydroxy-3-(*S*)-(*n*-butyl)-3-[2-(*S*)-((3,4-dichlorophenyl)amino-carbonyl)pyrrolidin-1-carbonyl]-2-(*S*)-fluoropropionamide



The title compound was prepared according to General Procedure H from 3,4-dichloroaniline. ^{1}H NMR ($CDCl_3$): δ 7.94 (s, 1H), 7.48–7.46 (m, 2H), 5.38–5.21 (dd, J = 4.4 Hz, $J_{H,F}$ = 47 Hz, 1H), 4.73–4.71 (m, 1H), 3.92–3.91 (m, 2H), 3.53–3.52 (m, 1H), 2.53–1.97 (m, 6H), 1.59–1.58 (m, 4H), 1.09 (t, J = 6.9 Hz, 3H). ES-MS: calcd. For $C_{19}H_{24}Cl_2FN_3O_4S$ (447.11); found: 448.2 [M+1].

Example 80

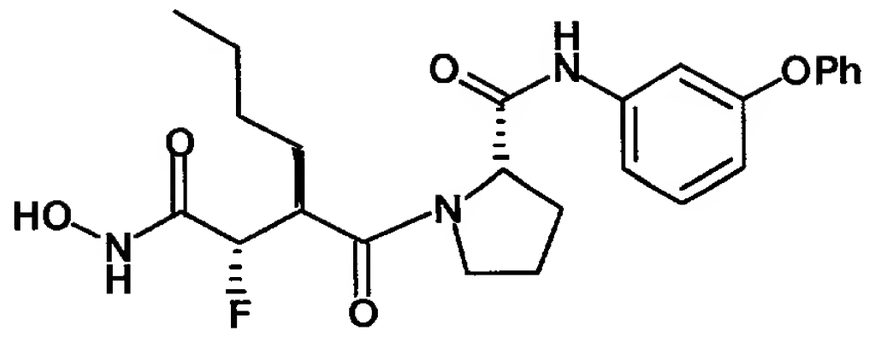
Synthesis of *N*-hydroxy-3-(*S*)-(*n*-butyl)-3-[2-(*S*)-((benzthiazol-2-yl)amino-carbonyl)pyrrolidin-1-carbonyl]-2-(*S*)-fluoropropionamide



The title compound was prepared according to General Procedure H from 2-aminobenzothiazole. ^{1}H NMR ($CDCl_3$): δ 7.66 (t, J = 7.7 Hz, 2H), 7.34 (t, J = 6.9 & 7.9 Hz, 1H), 7.26 (t, J=7.7 & 7.4 Hz, 1H), 5.10–5.92 (dd, J = 5.8 Hz; $J_{H,F}$ = 47 Hz, 1H), 4.75–4.73 (m, 1H), 3.75–3.70 (m, 2H), 3.30–3.21 (m, 1H), 2.24–1.97 (m, 4H), 1.70–1.56 (m, 2H), 1.33–1.25 (m, 4H), 0.78 (t , J = 6.8 Hz, 3H). ES-MS: calcd. For $C_{20}H_{25}F N_4O_4S$ (436.50); found: 437.3 [M + 1].

Example 81

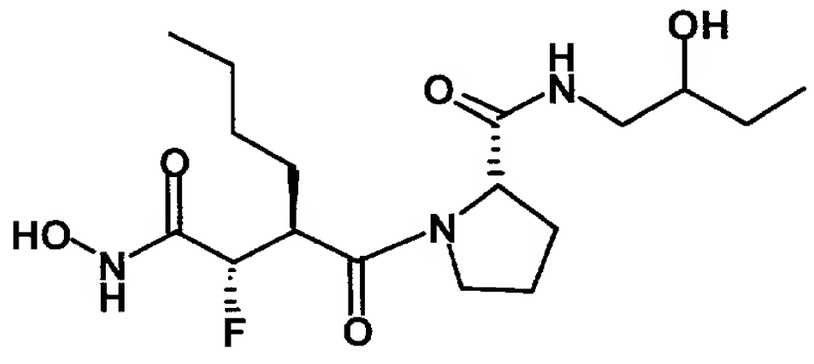
Synthesis of *N*-hydroxy-3-(*S*)-(*n*-butyl)-3-[2-(*S*)-((3-phenoxyphenyl)amino-carbonyl)pyrrolidin-1-carbonyl]-2-(*S*)-fluoropropionamide



The title compound was prepared according to General Procedure H from 3-phenoxyaniline. ^{1}H NMR ($CDCl_3$): δ 7.62–7.51 (m, 5H), 7.50–7.43 (m, 1H), 7.42–7.30 (m, 1H), 7.28–7.16 (m, 2H), 6.90–6.86 (m, 1H), 5.32–5.14 (dd, J = 5.3 Hz, $J_{H,F}$ = 47 Hz, 1H), 4.76–4.74 (m, 1H), 3.89–3.87 (m, 2H), 3.51–3.41 (m, 1H), 2.47–1.92 (m, 6H), 1.53–1.51 (m, 4H), 1.05 (t, J = 6.9 & 7.1 Hz, 3H). ES-MS: calcd. For $C_{25}H_{30}FN_3O_5$ (471.52); found: 472.4 [M+1].

Example 82

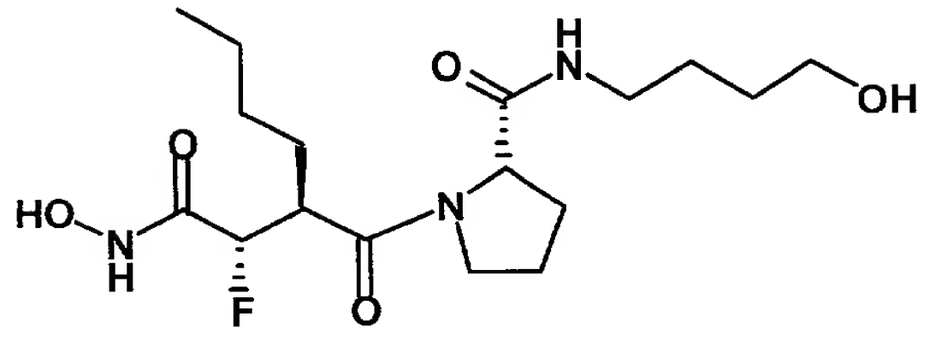
Synthesis of *N*-hydroxy-3-(*S*)-(*n*-butyl)-3-[2-(*S*)-((2-(*RS*)-hydroxybutyl)amino-carbonyl)pyrrolidin-1-carbonyl]-2-(*S*)-fluoropropionamide



The title compound was prepared according to General Procedure H from (±)-2-hydroxy-*n*-butylamine. ^{1}H NMR (CD_3OD): δ 5.09–4.92 (dd, J = 8.8 Hz, $J_{H,F}$ = 47 Hz, 1H), 4.63–4.59 (m, 1H), 4.03–3.90 (m, 1H), 3.88–3.79 (m, 1H), 3.76–3.73 (m, 1H), 3.51 (s, 2H), 3.46–3.23 (m, 1H), 2.41–2.14 (m, 4H), 1.79–1.52 (m, 8H), 1.17 (t, J = 7.3 Hz, 3H), 1.11 (t, J = 6 & 7.4 Hz, 3H). ES-MS: calcd. For $C_{17}H_{30}F N_3O_5$ (375.44); found: 376.4 [M+1].

Example 83

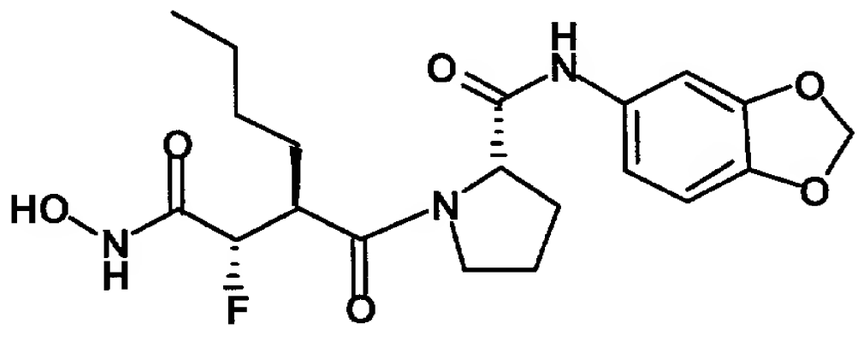
Synthesis of *N*-hydroxy-3-(*S*)-(*n*-butyl)-3-[2-(*S*)-((4-hydroxybutyl)amino-carbonyl)pyrrolidin-1-carbonyl]-2-(*S*)-fluoropropionamide



The title compound was prepared according to General Procedure H from 4-aminobutanol. ^{1}H NMR (CD_3OD): δ 5.07–4.90 (dd, J = 8.8 Hz, $J_{H,F}$ = 47 Hz, 1H), 4.60–4.55 (dd, J = 4.5 & 4.9 Hz, 1H), 4.05–3.92 (m, 1H), 3.90–3.81 (m, 1H), 3.76 (s, 2H), 3.51 (s, 2H), 3.44–3.38 (m, 1H), 2.44–2.10 (m, 6H), 1.86–1.63 (m, 4H), 1.60–1.52 (m, 2H), 1.14 (t , J = 6.8 Hz, 3H). ES-MS: calcd. For $C_{17}H_{30}F N_3O_5$ (375.44); found: 376.4 [M+1].

Example 84

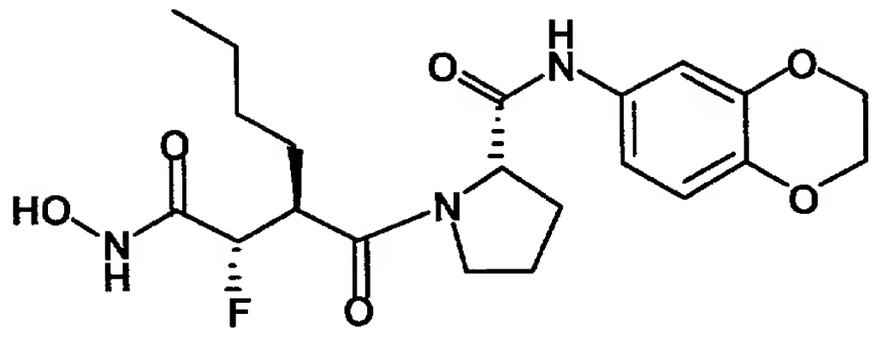
Synthesis of *N*-hydroxy-3-(*S*)-(*n*-butyl)-3-[2-(*S*)-((3,4-methylenedioxyphenyl)amino-carbonyl)pyrrolidin-1-carbonyl]-2-(*S*)-fluoropropionamide



The title compound was prepared according to General Procedure H from 3,4-(methylenedioxy)aniline. ^{1}H NMR ($CDCl_3$): 7.19 (s, 1H), 6.86 (d, J = 8 Hz, 1H), 6.67 (d, J = 8 Hz, 1H), 5.89 (s, 2H), 5.13–4.96 (dd, J = 4.4 Hz, $J_{H,F}$ = 47 Hz, 1H), 4.55–4.53 (m, 1H), 3.76-3.72 (m,2H), 3.30–3.21 (dd, J = 4.1 Hz, 1H), 2.26–2.24 (m, 2H), 2.01–1.95 (m, 2H), 1.73 (bs, 2H), 1.32 (bs, 4H), 0.86 (t, J = 6.3 Hz, 3H). ES-MS: calcd. For $C_{20}H_{26}FN_3O_6$ (423.44); found: 424.3 [M+1].

Example 85

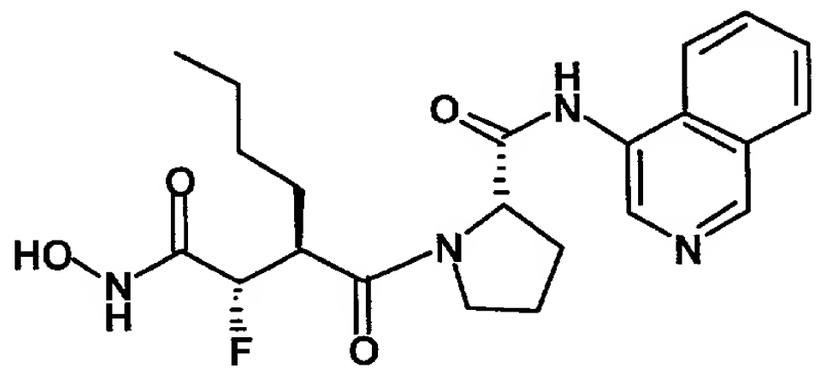
Synthesis of *N*-hydroxy-3-(*S*)-(*n*-butyl)-3-[2-(*S*)-((1,4-benzodioxan-6-yl)amino-carbonyl)pyrrolidin-1-carbonyl]-2-(*S*)-fluoropropionamide



The title compound was prepared according to General Procedure H from 1,4-benzodioxan-6-amine. ^{1}H NMR ($CDCl_3$): δ 7.14 (s, 1H), 6.93 (d, J = 8.5 Hz, 1H), 6.74, (d, J = 8.5 Hz, 1H), 5.14–4.97 (dd, J = 4.5 Hz, $J_{H,F}$ = 47 Hz, 1H), 4.58–4.56 (m, 1H), 4.20 (s, 4H), 3.73–3.64 (m2H), 3.49–3.21 (m, 1H), 2.30–2.27 (m, 2H), 2.01–1.94 (m, 2H), 1.74 (bs, 2H), 1.32 (bs, 4H), 0.85 (t, J = 6.6 & 7.1 Hz, 3H). ES-MS: calcd. For $C_{21}H_{28}FN_3O_6$ (437.46); found: 438.3 [M+1].

Example 86

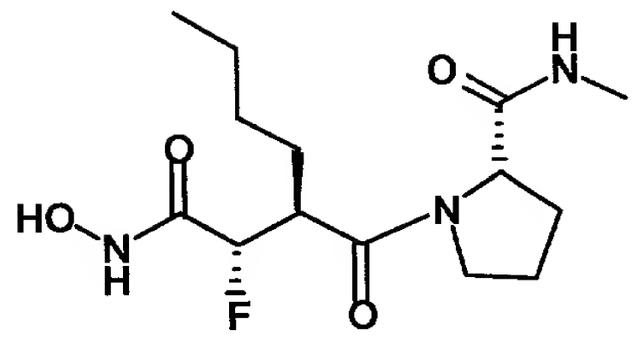
Synthesis of *N*-hydroxy-3-(*S*)-(*n*-butyl)-3-[2-(*S*)-((isoquinolin-3-yl)amino-carbonyl)pyrrolidin-1-carbonyl]-2-(*S*)-fluoropropionamide



The title compound was prepared according to General Procedure H from 6-aminoisoquinoline. ^{1}H NMR ($CDCl_3$): δ 9.89 (s, 1H), 9.63 (s, 1H), 7.85 (d, J = 8.5 Hz, 1H), 7.71 (m, 2H), 7.61 (d, J = 8.5 Hz, 1H), 5.16–4.99 (dd, J = 5.8 Hz, $J_{H,F}$ = 47 Hz, 1H), 4.76–4.73 (m, 1H), 3.85 (m, 2H), 3.41–3.25 (m, 1H), 2.35–1.99 (m, 4H), 1.33–1.25 (m, 6H), 0.85 (t, J = 6.8 & 7.1 Hz, 3H). ES-MS: calcd. For $C_{22}H_{27}FN_4O_4$ (430.47); found: 431.3 [M+1].

Example 87

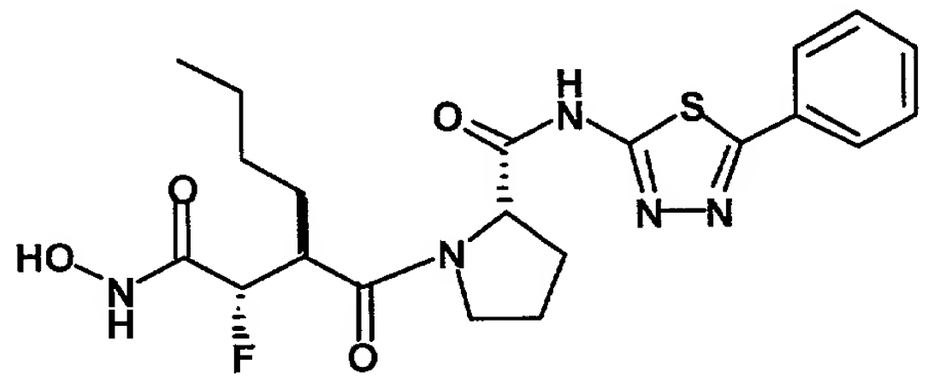
Synthesis of *N*-hydroxy-3-(*S*)-(*n*-butyl)-3-[2-(*S*)-(methylaminocarbonyl)pyrrolidin-1-carbonyl]-2-(*S*)-fluoropropionamide



The title compound was prepared according to General Procedure H from methylamine. ^{1}H NMR (CD_3OD): δ 5.064.90 (dd, J = 8.7 Hz, $J_{H,F}$ = 47 Hz, 1H), 4.58–4.54 (dd, J = 5 Hz, 1H), 4.05–4.00 (m, 1H), 3.99–3.82 (m, 1H), 3.50–3.49 (m, 1H), 2.93 (s, 3H), 2.40–2.08 (m, 4H), 1.79–1.51 (m, 6H), 1.21 (t, J = 6.8 Hz, 3H). ES-MS: calcd. For $C_{14}H_{24}FN_3O_4$ (317.36); found: 318.3 [M+1].

Example 88

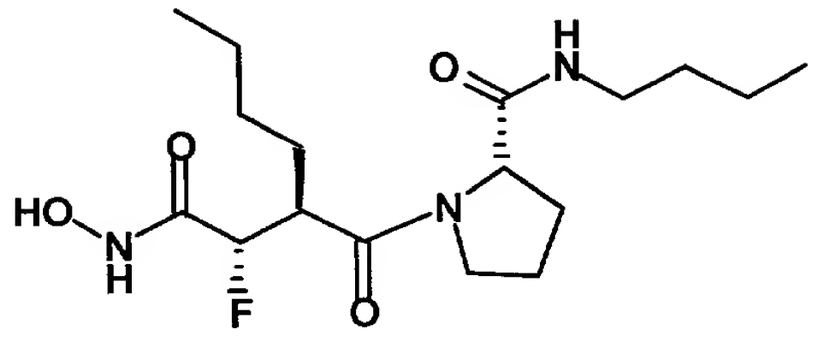
Synthesis of *N*-hydroxy-3-(*S*)-(*n*-butyl)-3-[2-(*S*)-((5-phenylthiadiazol-2-yl)amino-carbonyl)pyrrolidin-1-carbonyl]-2-(*S*)-fluoropropionamide



The title compound was prepared according to General Procedure H from 2-amino-5-phenylthiadiazole. ^{1}H NMR ($CDCl_3$ + DMSO-D6): δ 7.47–7.34 (m, 5H), 5.06–5.03 (dd, J = 7.7 Hz, $J_{H,F}$ = 47 Hz, 1H), 5.02–4.87 (m, 1H), 3.80–3.71 (m, 2H), 3.31–3.28 (m, 1H), 2.18-2.12 (m, 4H), 1.73–1.33 (m, 6H), 0.87 (t, J = 6.7 Hz, 3H). ES-MS: calcd. For $C_{21}H_{26}FN_5O_4S$ (463.53); found: 464.2 [M+1].

Example 89

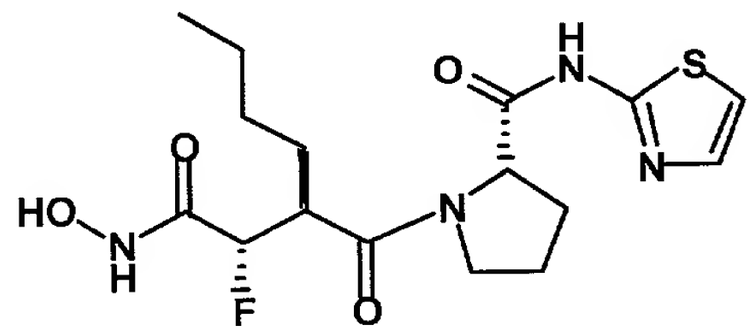
Synthesis of *N*-hydroxy-3-(*S*)-(*n*-butyl)-3-[2-(*S*)-(*n*-butylaminocarbonyl)pyrrolidin-1-carbonyl]-2-(*S*)-fluoropropionamide



The title compound was prepared according to General Procedure H from *n*-butylamine. ^{1}H NMR ($CDCl_3$): δ 7.21 (t, J = 6.5 & 5.5 Hz, 1H), 5.14–4.97 (dd, J = 5.8 Hz, $J_{H,F}$ = 47 Hz, 1H), 3.65–3.57 (m, 2H), 3.30–3.16 (m, 3H), 2.23–2.17 (m, 2H), 1.97–1.72 (m, 2H), 1.69–1.50 (m, 2H), 1.48–1.25 (m, 8H), 0.92–0.87 (m, 6H). ES-MS: calcd. For $C_{17}H_{30}FN_3O_4$ (359.44); found: 360.3 [M+1].

Example 90

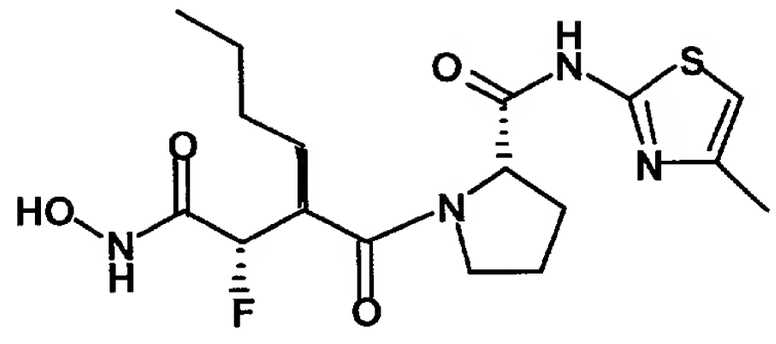
Synthesis of *N*-hydroxy-3-(*S*)-(*n*-butyl)-3-[2-(*S*)-((thiazol-2-yl)amino-carbonyl)pyrrolidin-1-carbonyl]-2-(*S*)-fluoropropionamide



The title compound was prepared according to General Procedure H from 2-aminothiazole. ^{1}H NMR ($CDCl_3$ + DMSO-D6): δ 7.40 (d, J = 3.6 Hz, 1H), 6.95 (d, J = 3.6 Hz, 1H), 5.05–4.88 (dd, J = 7.4 Hz, $J_{H,F}$ = 47 Hz, 1H), 4.86–4.84 (m, 1H), 3.84–3.71 (m, 2H), 3.33–3.23 (m, 1H), 2.16–1.99 (m, 4H), 1.72–1.30 (m, 6H), 0.84 9 (t, J = 6.8 & 7.1 Hz, 3H). ES-MS: calcd. For $C_{16}H_{23}FN_4O_4S$ (386.44); found: 387.4 [M+1].

Example 91

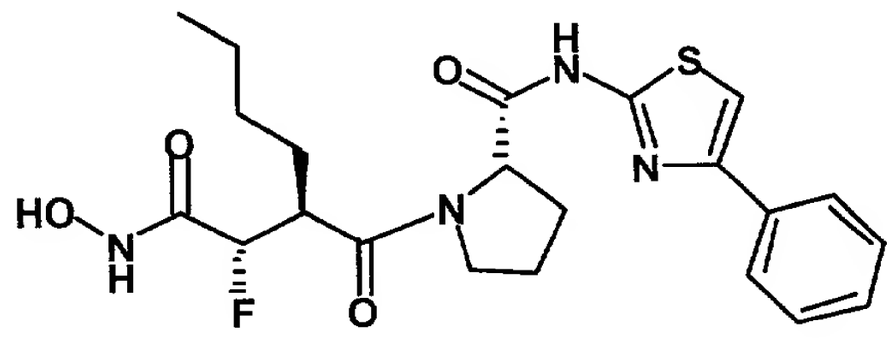
Synthesis of *N*-hydroxy-3-(*S*)-(*n*-butyl)-3-[2-(*S*)-((4-methylthiazol-2-yl)amino-carbonyl)pyrrolidin-1-carbonyl]-2-(*S*)-fluoropropionamide



The title compound was prepared according to General Procedure H from 2-amino-4-methylthiazole. ^{1}H NMR ($CDCl_3$ + DMSO-D6): δ 6.49 (s, 1H), 5.10–4.92 (dd, J = 6.6 Hz, $J_{H,F}$ = 47 Hz, 1H), 4.85–4.83 (m, 1H), 3.79–3.68 (m, 2H), 3.37–3.23 (m, 1H), 2.31 (s, 3H), 2.22–1.99 (m, 4H), 1.74–1.52 (m, 2H), 1.29–1.27 (m, 4H), 0.83 (t, J = 6.6 & 7.1 Hz, 3H). ES-MS: calcd. For $C_{17}H_{25}FN_4O_4S$ (400.47); found: 401.6 [M+1].

Example 92

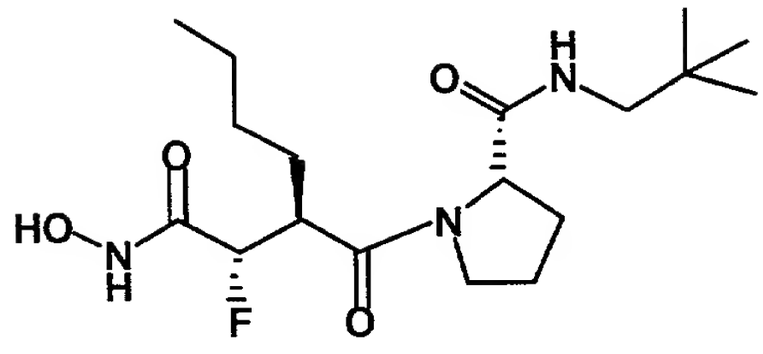
Synthesis of *N*-hydroxy-3-(*S*)-(*n*-butyl)-3-[2-(*S*)-((4-phenylthiazol-2-yl)amino-carbonyl)pyrrolidin-1-carbonyl]-2-(*S*)-fluoropropionamide



The title compound was prepared according to General Procedure H from 2-amino-4-phenylthiazole. ^{1}H NMR ($CDCl_3$): δ 7.38–7.26 (m, 5H), 6.95 (s, 1H), 5.15–5.01 (dd, J = 4.2 Hz, $J_{H,F}$ = 47Hz, 1H), 4.99–4.83 (m, 1H), 3.76–3.70 (m, 2H), 3.31–3.27 (m, 1H), 2.15–1.99 (m, 4H), 1.72–1.50 (m, 2H), 1.44–1.25 (m, 4H), 0.81 (t, J = 6.6 & 7.1 Hz, 3H). ES-MS: calcd. For $C_{22}H_{27}FN_4O_4S$ (462.54); found: 463.5 [M+1].

Example 93

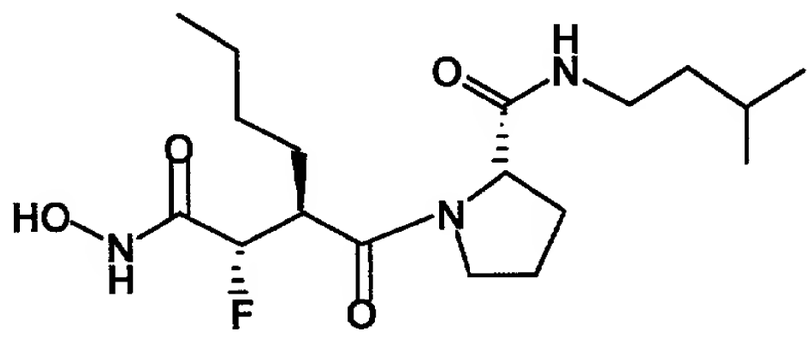
Synthesis of *N*-hydroxy-3-(*S*)-(*n*-butyl)-3-[2-(*S*)-((2,2-dimethylpropyl)amino-carbonyl)pyrrolidin-1-carbonyl]-2-(*S*)-fluoropropionamide



The title compound was prepared according to General Procedure H from 2,2-dimethylpropylamine. ^{1}H NMR ($CDCl_3$): δ 7.16 (t, J = 6 Hz, 1H), 5.14–4.96 (dd, J = 6.1 Hz, $J_{H,F}$ = 47 Hz, 1H), 4.55–4.48 (m, 1H), 3.69–3.61 (m, 2H), 3.31–3.22 (m, 1H), 3.14–3.07 (m, 1H), 2.98–2.91 (m, 1H), 2.24–1.96 (m, 4H), 1.72–1.63 (m, 2H), 1.33–1.30 (m, 4H), 0.88 (m, 12H). ES-MS: calcd. For $C_{18}H_{32}FN_3O_4$ (373.46); found: 374.7 [M+1].

Example 94

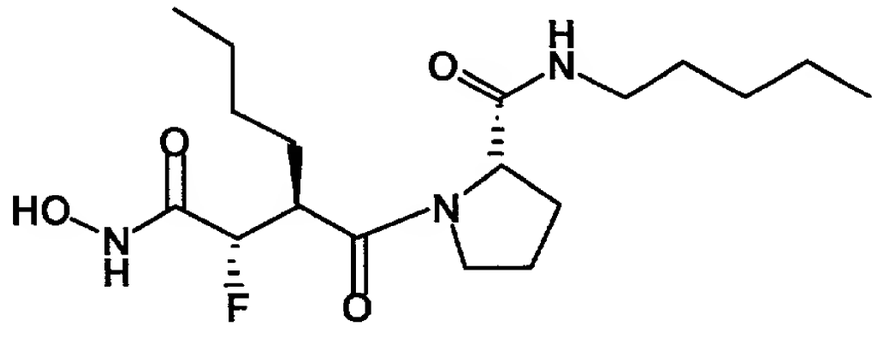
Synthesis of *N*-hydroxy-3-(*S*)-(*n*-butyl)-3-[2-(*S*)-((3-methylbutyl)amino-carbonyl)pyrrolidin-1-carbonyl]-2-(*S*)-fluoropropionamide



The title compound was prepared according to General Procedure H from 3-methylbutylamine. ^{1}H NMR ($CDCl_3$): δ 7.17 (t, J = 5.2 Hz, 1H), 5.13–4.95 (dd, J = 6.1 Hz, $J_{H,F}$ = 47 Hz, 1H), 4.47–4.44 (m, 1H), 3.66–3.57 (m, 2H), 3.31–3.17 (m, 3H), 2.23–2.17 (m, 2H), 1.96–1.91 (m, 2H), 1.74–1.54 (m, 3H), 1.42–1.32 (m, 6H), 0.91–0.87 (m, 9H). ES-MS: calcd. For $C_{18}H_{32}FN_3O_4$ (373.46); found: 374.7 [M+1].

Example 95

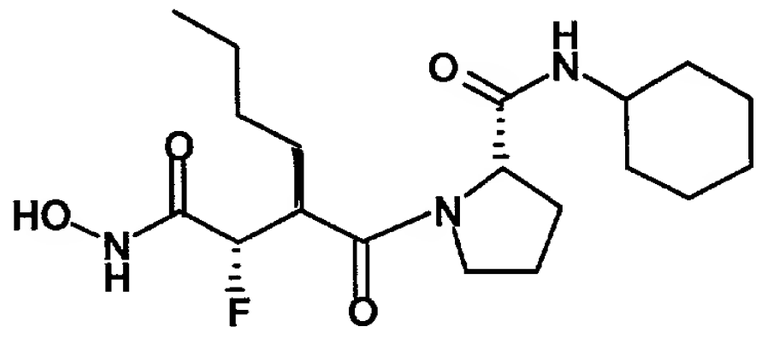
Synthesis of *N*-hydroxy-3-(*S*)-(*n*-butyl)-3-[2-(*S*)-((*n*-pentyl)amino-carbonyl)pyrrolidin-1-carbonyl]-2-(*S*)-fluoropropionamide



The title compound was prepared according to General Procedure H from amylamine. ^{1}H NMR ($CDCl_3$): δ 7.18 (t, J = 5.2 Hz, 1H), 5.13–4.95 (dd, J = 6 Hz, $J_{H,F}$ = 47 Hz, 1H), 4.47–4.45 (m, 1H), 3.66–3.64 (m, 2H), 3.31–3.14 (m, 3H), 2.23–2.17 (m, 2H), 1.96–1.93 (m, 2H), 1.76–1.63 (m, 2H), 1.52–1.42 (m, 3H),1.34–1.26 (m, 8H), 0.91–0.85 (m, 6H). ES-MS: calcd. For $C_{18}H_{32}FN_3O_4$ (373.46); found: 374.7 [M+1].

Example 96

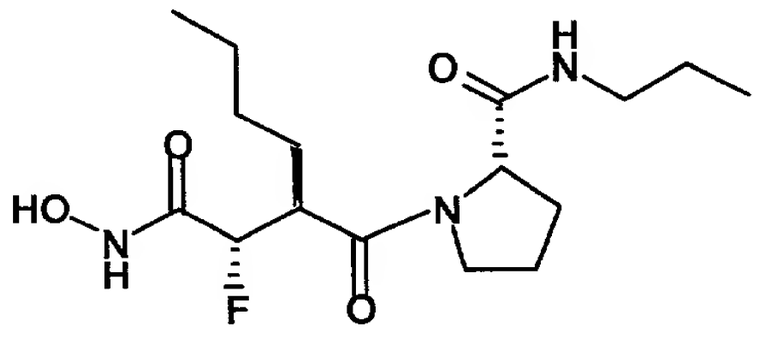
Synthesis of *N*-hydroxy-3-(*S*)-(*n*-butyl)-3-[2-(*S*)-((cyclohexyl)amino-carbonyl)pyrrolidin-1-carbonyl]-2-(*S*)-fluoropropionamide



The title compound was prepared according to General Procedure H from cyclohexylamine. ^{1}H NMR ($CDCl_3$): δ 7.00 (d, J = 8.2 Hz, 1H), 5.14–4.96 (dd, J = 6.2 Hz, $J_{H,F}$ = 47 Hz, 1H), 4.46–4.44 (m, 1H), 3.73–3.59 (m, 3H), 3.31–3.22 (m, 1H), 2.19–2.10 (m, 4H), 1.96–1.64 (m, 6H), 1.33–1.27 (m, 6H), 1.20–1.12 (m, 4H), 0.89 (t, J = 6.6 Hz, 3H). ES-MS: calcd. For $C_{19}H_{32}FN_3O_4$ (385.47); found: 386.7 [M+1].

Example 97

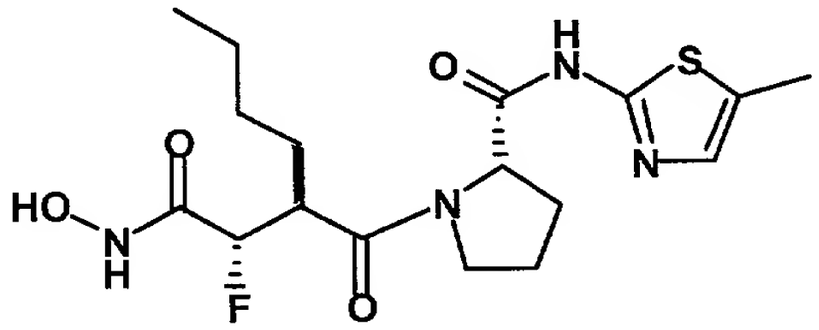
Synthesis of *N*-hydroxy-3-(*S*)-(*n*-butyl)-3-[2-(*S*)-((*n*-propyl)amino-carbonyl)pyrrolidin-1-carbonyl]-2-(*S*)-fluoropropionamide



The title compound was prepared according to General Procedure H from propylamine. ^{1}H NMR ($CDCl_3$ + DMSO–D6): δ 7.24 (t, J = 5.2 Hz, 1H), 4.99–4.80 (dd, J = 8.8 Hz, $J_{H,F}$ = 47 Hz, 1H), 4.59–4.57 (m, 1H), 3.72–3.56 (m, 2H), 3.37–3.12 (m, 3H), 2.31–2.26 (m, 2H), 2.09–1.84 (m, 4H), 1.66–1.43 (m, 2H), 1.28–1.03 (m, 4H), 0.91–0.87 (m, 6H). ES-MS: calcd. For $C_{16}H_{28}FN_3O_4$ (345.41); found: 346.6 [M+1].

Example 98

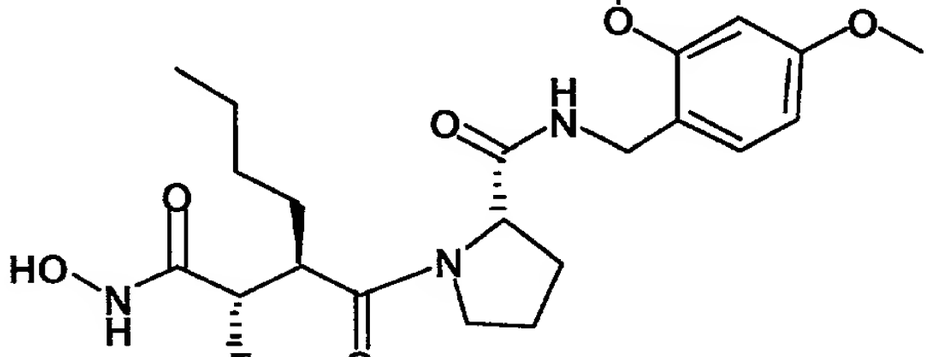
Synthesis of *N*-hydroxy-3-(*S*)-(*n*-butyl)-3-[2-(*S*)-((5-methylthiazol-2-yl)amino-carbonyl)pyrrolidin-1-carbonyl]-2-(*S*)-fluoropropionamide



The title compound was prepared according to General Procedure H from 2-amino-5-methylthiazole. ^{1}H NMR ($CDCl_3$): δ 7.31 (s, 1H), 5.32–5.14 (dd, J = 6.1 Hz, $J_{H,F}$ = 47 Hz, 1H), 4.8–4.83 (m, 1H), 4.03–3.94 (m, 2H), 3.53–3.44 (m, 1H), 2.62 (s, 3H), 2.58–2.21 (m, 4H), 1.99–1.78 (m, 2H), 1.54–1.45 (m, 4H), 1.08 (t, J = 6.6 & 7.4 Hz, 3H). ES-MS: calcd. For $C_{17}H_{25}FN_4O_4S$ (400.47); found: 401.6 [M+1].

Example 99

Synthesis of *N*-hydroxy-3-(*S*)-(*n*-butyl)-3-[2-(*S*)-((3,4-dimethoxybenzyl)amino-carbonyl)pyrrolidin-1-carbonyl]-2-(*S*)-fluoropropionamide

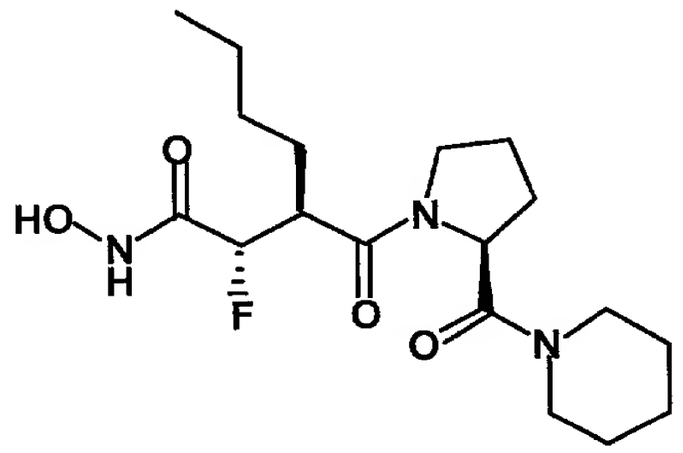


The title compound was prepared according to General Procedure H from 2,4-dimethoxybenzylamine. ^{1}H NMR ($CDCl_3$): δ 7.31 (d, J = 8 Hz, 1H), 6.67–6.58 (m, 2H), 5.30–5.14 (dd, J = 2 Hz, $J_{H,F}$ = 47 Hz, 1H), 4.67–4.45 (m, 3H), 4.00 (s, 3H), 3.98

(s, 3H), 3.86–3.78 (m, 2H), 3.45–3.39 (m, 1H), 2.37–2.13 (m, 4H), 1.89–1.84 (m, 2H), 1.47–1.45 (m, 4H), 1.04 (t, J = 6.3 & 7.1 Hz, 3H). ES-MS: calcd. For $C_{22}H_{32}FN_3O_6$ (453.51); found: 454.8 [M+1].

Example 100

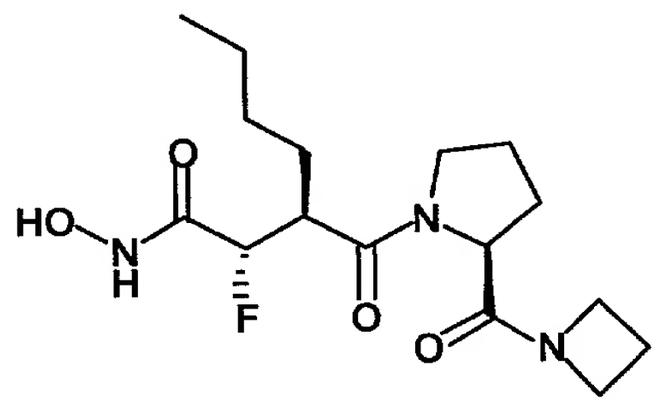
Synthesis of *N*-hydroxy-3-(*S*)-(*n*-butyl)-3-[2-(*S*)-(piperidin-1-ylcarbonyl)pyrrolidin-1-carbonyl]-2-(*S*)-fluoropropionamide



The title compound was prepared according to General Procedure H from piperidine. ^{1}H NMR (CDCl3): δ 5.14-4.97 (dd, J = 6.5Hz, $J_{H,F}$ = 47 Hz, 1H), 4.91-4.87 (m, 1H), 3.80-3.47 (m, 6H), 3.39-3.21 (m, 1H), 2.22-1.83 (m, 3H), 1.65-1.27 (m, 13H), 0.90 (t, J = 7 Hz, 3H). ES-MS: calcd. For $C_{18}H_{30}FN_3O_4$(371.45); found: 372.4 [M+1].

Example 101

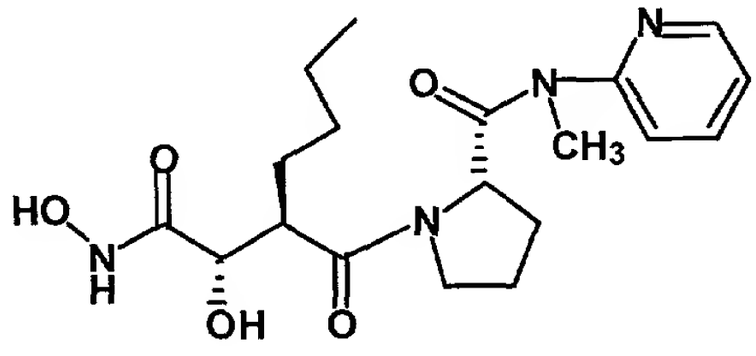
Synthesis of *N*-hydroxy-3-(*S*)-(*n*-butyl)-3-[2-(*S*)-(azetidin-1-ylcarbonyl)pyrrolidin-1-carbonyl]-2-(*S*)-fluoropropionamide



The title compound was prepared according to General Procedure H from azetidine. ^{1}H NMR (CD_3OD): δ 5.10-4.92 (dd, J = 8.7 Hz, $J_{H,F}$ = 47 Hz, 1H), 4.73-4.65 (m, 1H), 4.60-4.57 (m, 1H), 4.49-4.41 (m, 1H), 4.32-4.21 (m, 1H), 4.18-4.12 (m, 1H), 4.06-3.99 (m, 1H), 3.89-3.81 (m, 1H), 2.59-2.41 (m, 2H), 2.41-2.30 (m, 2H), 2.28-2.05 (m, 2H), 1.84-1.49 (m, 6H), 1.11 (t, J = 7 Hz, 3H). ES-MS: calcd. For $C_{16}H_{26}FN_3O_4$ (343.39); found: 344.4 [M+1].

Example 102

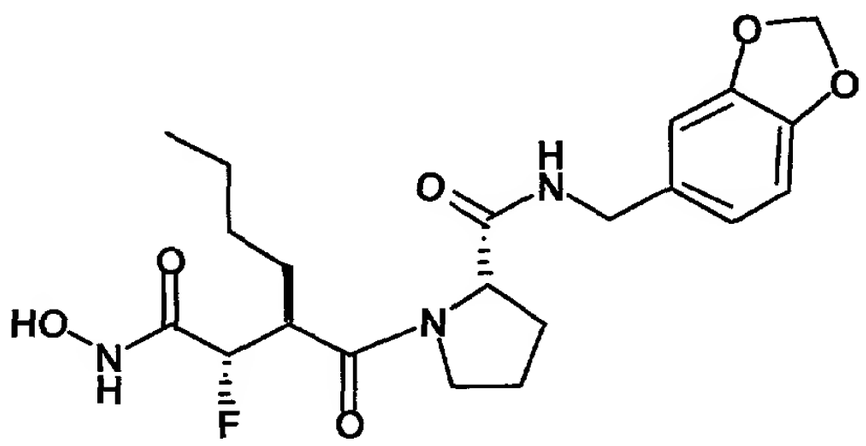
Synthesis of *N*-hydroxy-3-(*R*)-(*n*-butyl)-3-[2-(*S*)-((N-pyridin-2-yl)methylamino-carbonyl)-pyrrolidin-1-carbonyl]-2-(*S*)-hydroxypropionamide



The title compound was prepared according to General Procedure F from N-methyl-2-amino pyridine. ^{1}H NMR ($CDCl_3$): δ 8.75-8.04 (m, 2H),7.71-7.46 (m,2H), 4.76 bs, 1H), 4.46 (bs, 1H), 3.93-3.63 (m, 2H), 3.56 (s,3H), 3.42-3.39 (m, 1H), 2.28-2.00 (m, 6H), 1.66-1.62 (m, 4H), 1.13 (t, J = 7 Hz, 3H). ES-MS: calcd. For $C_{19}H_{28}N_4O_5$ (392.45); found: 393.6 [M+1].

Example 103

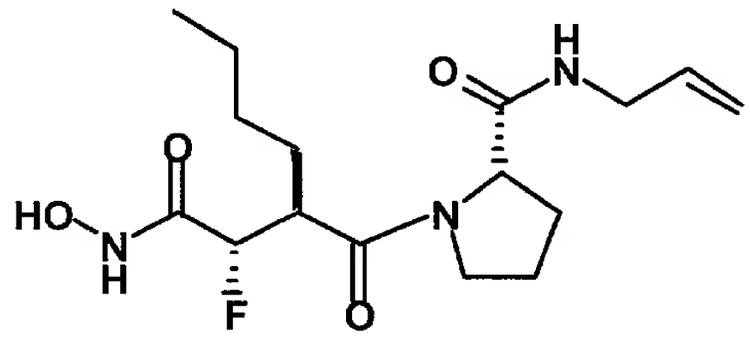
Synthesis of *N*-hydroxy-3-(*S*)-(*n*-butyl)-3-[2-(*S*)-((3,4-methylenedioxybenzyl)-aminocarbonyl)pyrrolidin-1-carbonyl]-2-(*S*)-fluoropropionamide



The title compound was prepared according to General Procedure H from piperonylamine. ^{1}H NMR ($CDCl_3$): 7.63(s, 1H), 6.93 (d, J = 9.9 Hz, 2H), 6.11 (s, 2H), 5.30–5.13 (dd, J = 5.5 Hz, $J_{H.F}$ = 47 Hz, 1H), 4.62–4.39 (m ,3H), 3.97–3.71 (m, 2H), 3.48–3.39 (m, 1H), 2.38–2.13 (m, 4H), 1.87–1.85 (m, 2H), 1.49–1.48 (m, 4H), 1.05 (t, J = 6.3 Hz, 3H). ES-MS: calcd. For $C_{21}H_{28}FN_3O_6$ (437.46); found: 438.7 [M+1].

Example 104

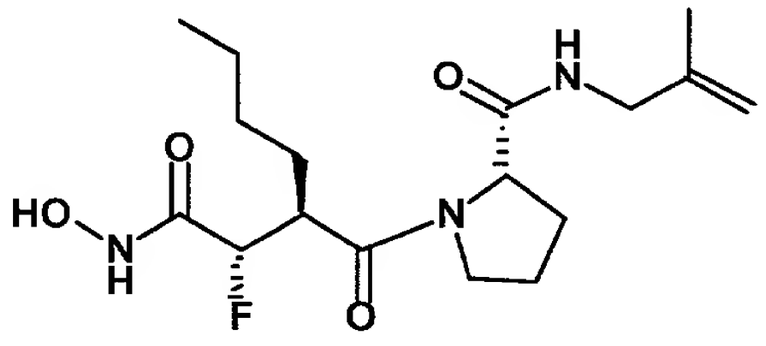
Synthesis of *N*-hydroxy-3-(*S*)-(*n*-butyl)-3-[2-(*S*)-((allyl)aminocarbonyl)pyrrolidin-1-carbonyl]-2-(*S*)-fluoropropionamide



The title compound was prepared according to General Procedure H from allylamine. ^{1}H NMR ($CDCl_3$): δ 6.06–5.95 (m, 1H), 5.39–5.17 (m, 3H), 4.69–4.67 (m, 1H), 4.05–3.85 (m, 4H), 3.51–3.44 (m, 1H), 2.40–2.17 (m, 4H), 1.91–1.89 (m, 2H), 1.62–1.53 (m, 4H), 1.09 (t, J = 6.3 Hz, 3H). ES-MS: calcd. For $C_{16}H_{26}FN_3O_4$ (343.39); found: 344.7 [M+1].

Example 105

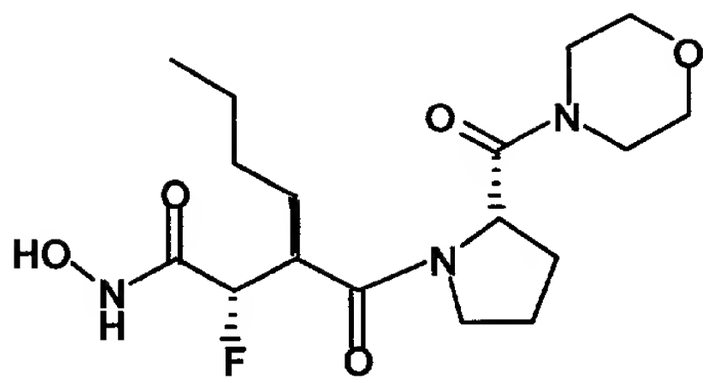
Synthesis of *N*-hydroxy-3-(*S*)-(*n*-butyl)-3-[2-(*S*)-((2-methylallyl)aminocarbonyl)-pyrrolidin-1-carbonyl]-2-(*S*)-fluoropropionamide



The title compound was prepared according to General Procedure H from 2-methylallylamine. ^{1}H NMR ($CDCl_3$): δ 5.34–5.16 (dd, J = 5.8 Hz, $J_{H,F}$ = 47 Hz, 1H), 5.00 (s, 2H) 4.73–4.66 (m, 1H), 4.05–3.87 (m, 4H), 3.51–3.43 (m, 1H), 2.43–2.17 (m, 4H), 1.90 (s, 3H), 1.86–1.84 (m, 2H), 1.66–1.53 (m, 4H), 1.08 (t, J = 6.6 Hz, 3H). ES-MS: calcd. For $C_{17}H_{28}FN_3O_4$ (357.42); found: 358.6 [M+1].

Example 106

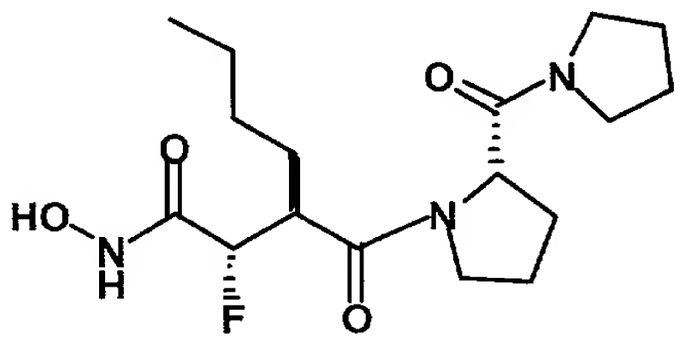
Synthesis of *N*-hydroxy-3-(*S*)-(*n*-butyl)-3-[2-(*S*)-(morpholin-4-ylcarbonyl)pyrrolidin-1-carbonyl]-2-(*S*)-fluoropropionamide



The title compound was prepared according to General Procedure H from morpholine. ^{1}H NMR ($CDCl_3$): δ 5.34–5.16 (dd, J = 6.2 Hz, $J_{H,F}$ = 47 Hz, 1H), 5.08–5.05 (m, 1H), 4.00–3.71 (m, 10H), 3.68–3.43 (m, 1H), 2.42–1.83 (m, 6H), 1.78–1.50 (m, 4H), 1.10 (t, J = 6.6 & 7.1 Hz, 3H). ES-MS: calcd. For $C_{17}H_{28}FN_3O_5$ (373.42); found: 374.5 [M+1].

Example 107

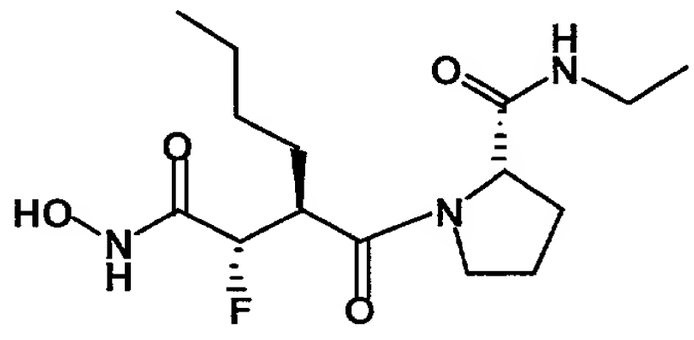
Synthesis of *N*-hydroxy-3-(*S*)-(*n*-butyl)-3-[2-(*S*)-(pyrrolidin-1-carbonyl)pyrrolidin-1-carbonyl]-2-(*S*)-fluoropropionamide



The title compound was prepared according to General Procedure H from pyrrolidine. ^{1}H NMR ($CDCl_3$): δ 5.34–5.17 (dd, J = 6.5 Hz, $J_{H,F}$ = 47 Hz, 1H), 4.86–4.82 (m, 1H), 3.94–3.89 (m, 4H), 3.77–3.71 (m, 1H), 3.64–3.42 (m, 2H), 2.38–2.20 (m, 2H), 2.18–1.74 (m, 8H), 1.65–1.48 (m, 4H), 1.10 (t, J = 6.9 & 7.2 Hz, 3H). ES-MS: calcd. For $C_{17}H_{28}FN_3O_4$ (357.42); found: 358.5 [M+1].

Example 108

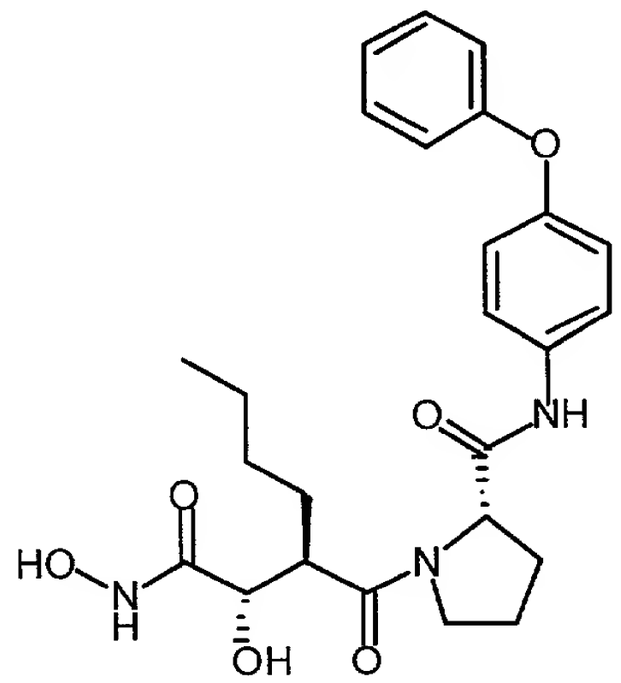
Synthesis of *N*-hydroxy-3-(*S*)-(*n*-butyl)-3-[2-(*S*)-((ethyl)aminocarbonyl)pyrrolidin-1-carbonyl]-2-(*S*)-fluoropropionamide



The title compound was prepared according to General Procedure H from ethylamine. ^{1}H NMR ($CDCl_3$): δ 5.35–5.19 (d, $J_{H,F}$ = 47 Hz, 1H), 4.64–4.60 (m, 1H), 3.85–3.78 (m, 2H), 3.45–3.19 (m, 3H), 2.44–2.13 (m, 4H), 1.93–1.84 (m, 2H), 1.55–1.38 (m, 4H), 1.30 (t, J = 7.2 Hz & 6.9 Hz, 3H), 1.10 (bs, 3H). ES-MS: calcd. For $C_{15}H_{26}FN_3O_4$ (331.38); found: 332.5 [M+1].

Example 109

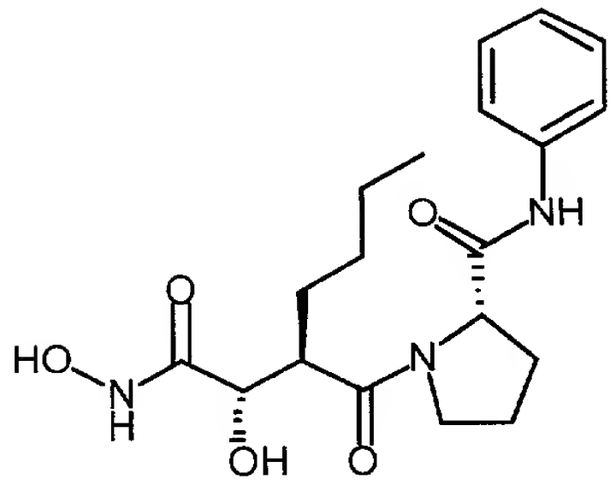
Synthesis of *N*-hydroxy-3-(*R*)-(*n*-butyl)-3-[2-(*S*)-((4-phenoxyphenyl)amino-carbonyl)pyrrolidin-1-carbonyl]-2-(*S*)-hydroxypropionamide



The title compound was prepared according to General Procedure F from 4-phenoxyaniline. ^{1}H NMR ($CDCl_3$): δ 7.48-6.92 (m, 9H), 4.55-4.53 (d, J = 6.0 Hz, 1H), 4.29-4.29 (d, J = 2.2 Hz, 1H), 3.73 (bs, 2H), 3.27 (bs, 1H), 2.29-1.78 (m, 6H), 1.41-1.36 (m, 4H), 0.89 (t, J = 6.6 & 7.14 Hz, 3H). ES-MS: calcd. For $C_{25}H_{31}N_3O_6$ (469.54); found: 470.4 [M+1].

Example 110

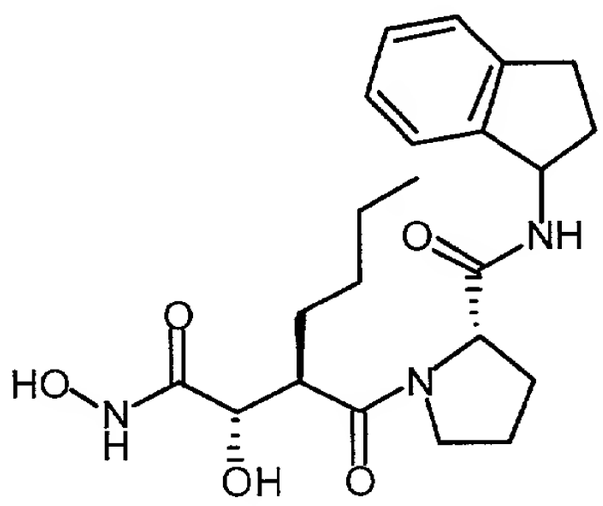
Synthesis of *N*-hydroxy-3-(*R*)-(*n*-butyl)-3-[2-(*S*)-((phenyl)aminocarbonyl)-pyrrolidin-1-carbonyl]-2-(*S*)-hydroxypropionamide



The title compound was prepared according to General Procedure F from aniline. ^{1}H NMR ($CDCl_3$): δ 7.52-7.03 (m, 6H), 4.58-4.55 (d, J = 8.0 Hz, 1H), 4.28-4.27 (d, J = 2.4 Hz, 1H), 3.71 (bs, 2H), 3.262 (bs, 1H), 2.31-1.77 (m, 6H), 1.41-1.33 (m, 4H), 0.89 (t, J = 6.6 & 7.4 Hz, 3H). ES-MS: calcd. For $C_{19}H_{27}N_3O_5$ (377.44); found: 378.3 [M+1].

Example 111

Synthesis of *N*-hydroxy-3-(*R*)-(*n*-butyl)-3-[2-(*S*)-((indan-1-yl)amino-carbonyl)pyrrolidin-1-carbonyl]-2-(*S*)-hydroxypropionamide

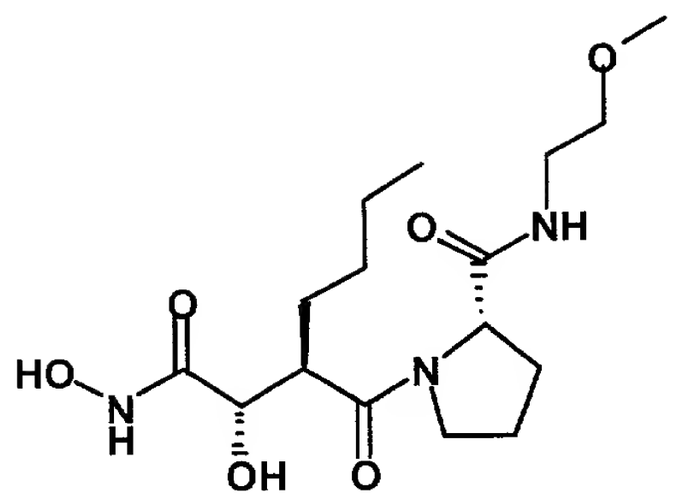


The title compound was prepared according to General Procedure F from 1-aminoindan. 1H NMR ($CDCl_3$): δ 7.27-7.15 (m, 4H), 5.38 (t, J = 8.2 & 7.7 Hz, 1H), 4.45 (bs, 1H), 4.18 (bs, 1H), 3.64 (m, 2H), 3.20-3.18 (m, 1H), 2.98-2.49 (m, 4H), 2.24-1.73 (m, 6H), 1.95-1.326 (m, 4H), 0.88 (t, J = 6.0 & 5.5 Hz, 3H).

ES-MS: calcd. For $C_{22}H_{31}N_3O_5$ (417.51); found: 418.4 [M+1]

Example 112

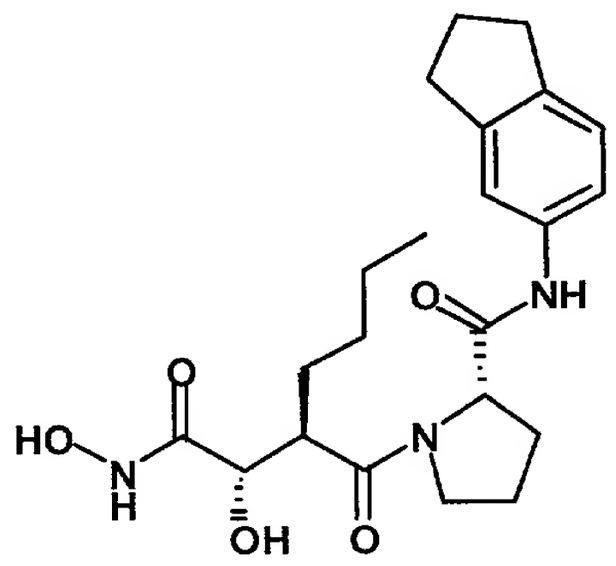
Synthesis of *N*-hydroxy-3-(*R*)-(*n*-butyl)-3-[2-(*S*)-((2-methoxyethyl)amino-carbonyl)pyrrolidin-1-carbonyl]-2-(*S*)-hydroxypropionamide



The title compound was prepared according to General Procedure F from 2-methoxyethylamine. ^{1}H NMR ($CDCl_3$): δ 4.45-4.27 (d, J = 6.87 Hz, 1H), 4.255 (bs, 1H), 3.69-3.29 (m, 9H), 2.15-1.77 (m, 6H), 1.43-1.3 (m, 4H), 0.92 (t, J = 6.593 & 6.867 Hz, 3H). ES-MS: calcd. For $C_{16}H_{29}N_3O_6$ (359.42); found: 360.3 [M+1].

Example 113

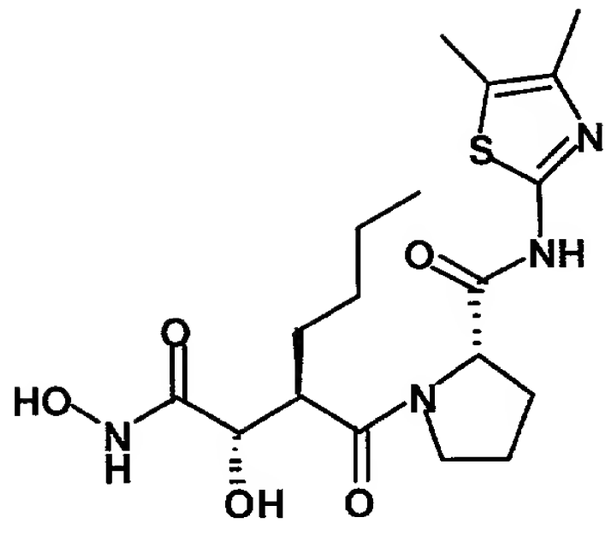
Synthesis of *N*-hydroxy-3-(*R*)-(*n*-butyl)-3-[2-(*S*)-((indan-5-yl)aminocarbonyl)-pyrrolidin-1-carbonyl]-2-(*S*)-hydroxypropionamide



The title compound was prepared according to General Procedure F from 5-aminoindan. ^{1}H NMR ($CDCl_3$): δ 7.46-7.08 (m, 3H), 4.57-4.55 (d, J = 67.14 Hz, 1H), 4.28 (bs, 1H), 3.71 (bs, 2H), 3.26 (bs, 1H), 2.87-2.79 (dd, J = 6.87 & 7.14 Hz, 4H), 2.3-1.77 (m, 8H), 1.35 (bs, 4H), 0.89 (t, J = 6.32 & 6.87 Hz, 3H). ES-MS: calcd. For $C_{22}H_{31}N_3O_5$ (417.51); found: 418.4 [M+1].

Example 114

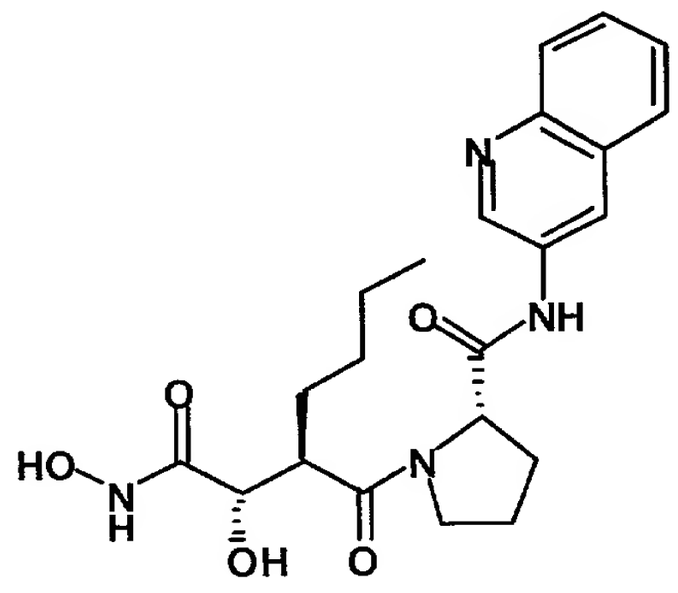
Synthesis of *N*-hydroxy-3-(*R*)-(*n*-butyl)-3-[2-(*S*)-((4,5-dimethylthiazol-2-yl)amino-carbonyl)-pyrrolidin-1-carbonyl]-2-(*S*)-hydroxypropionamide



The title compound was prepared according to General Procedure F from 2-amino-4,5-dimethylthiazole. ^{1}H NMR ($CDCl_3$): δ 4.60 (bs, 1H), 4.25 (bs, 1H), 3.79 (t, J = 5.77 & 4.67 Hz, 2H), 3.26 (bs, 1H), 2.30-2.24 (m, 8H), 1.74-2.12 (m, 4H), 1.36 (m, 4 H), 0.901 (t, J = 6.77 & 6.87 Hz, 3H). ES-MS: calcd. For $C_{18}H_{28}N_4O_5S$ (412.51); found: 413.3 [M+1].

Example 115

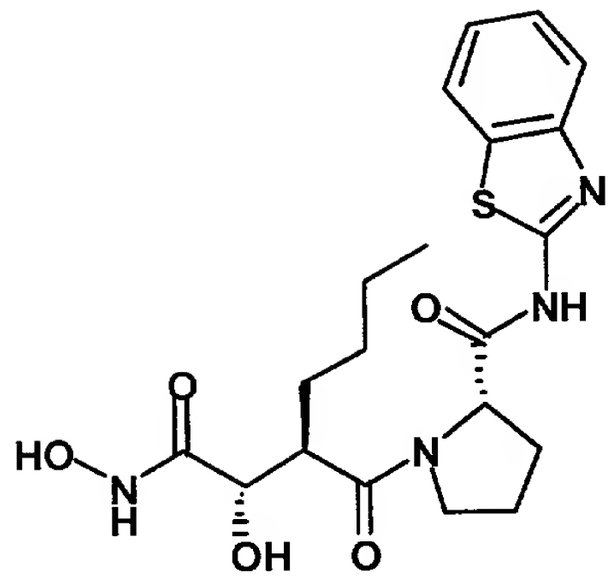
Synthesis of *N*-hydroxy-3-(*R*)-(*n*-butyl)-3-[2-(*S*)-((quinolin-3-yl)aminocarbonyl)-pyrrolidin-1-carbonyl]-2-(*S*)-hydroxypropionamide



The title compound was prepared according to General Procedure F from 3-aminoquinoline. ^{1}H NMR ($CDCl_3$): δ 8.17-7.26 (m, 6H), 4.68 (m, 1H), 4.32 (m, 1H), 3.77-3.67 (d, J = 30.217 Hz, 2H), 3.22 (bs, 1H), 2.17-1.69 (m, 6H), 1.30 (bs, 4H), 0.89-0.82 (m, 3H). ES-MS: calcd. For $C_{22}H_{28}N_4O_5$ (428.49); found: 429.3 [M+1].

Example 116

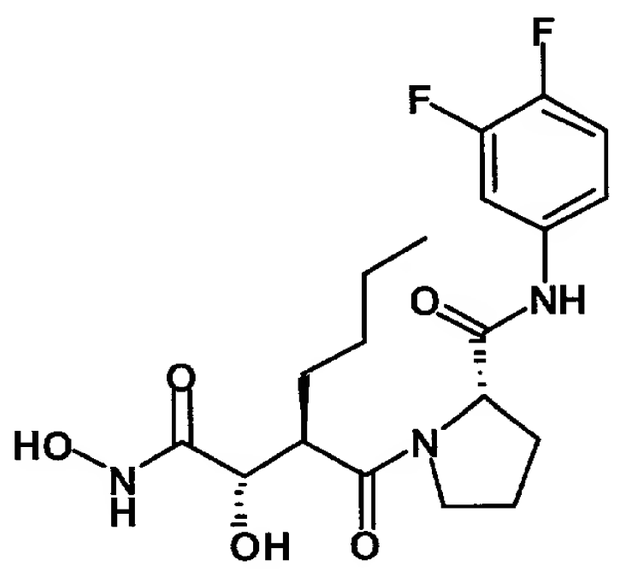
Synthesis of *N*-hydroxy-3-(*R*)-(*n*-butyl)-3-[2-(*S*)-((benzthiazol-2-yl)amino-carbonyl)-pyrrolidin-1-carbonyl]-2-(*S*)-hydroxypropionamide



The title compound was prepared according to General Procedure F from 2-aminobenzothiazole. ^{1}H NMR (DMSO-d6): δ 8.18-7.49 (m, 4H), 4.802 (bs, 1H), 3.98-3.94 (d, J = 9.066 Hz, 1H), 3.59 (bs, 2H), 3.11 (bs, 1H), 2.11-1.38 (m, 10H), 1.06-1.04 (m, 3H). ES-MS: calcd. For $C_{20}H_{26}N_4O_5S$ (434.52); found: 435.3 [M+1].

Example 117

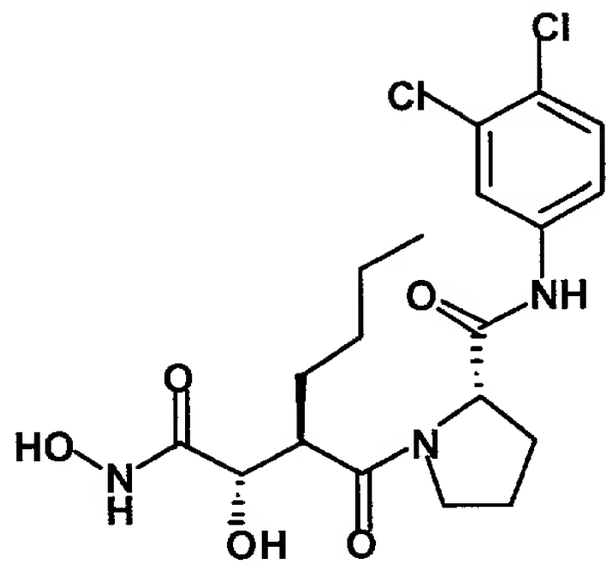
Synthesis of *N*-hydroxy-3-(*R*)-(*n*-butyl)-3-[2-(*S*)-((3,4-difluorophenyl)amino-carbonyl)-pyrrolidin-1-carbonyl]-2-(*S*)-hydroxypropionamide



The title compound was prepared according to General Procedure F from 3,4-difluoroaniline. ^{1}H NMR ($CDCl_3$): δ 7.60-6.97 (m, 3H), 4.49-4.61 (d, J = 7.97 Hz, 1H), 4.29-4.28 (d, J = 2.2 Hz, 1H), 3.79-3.69 (m, 2H), 3.26 (bs, 1H), 2.36-1.76 (m, 6H), 1.49-1.35 (m, 4H), 0.918 (t, J = 6.867 & 7.143 Hz, 3H). ES-MS: calcd. For $C_{19}H_{25}F_2N_3O_5$ (413.42); found: 414.3 [M+1].

Example 118

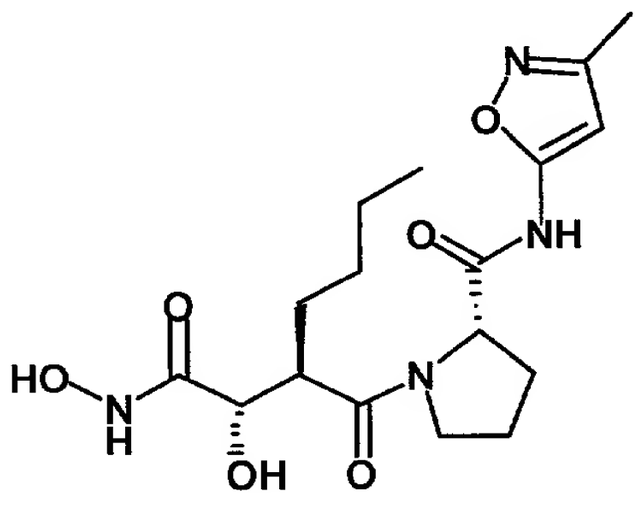
Synthesis of *N*-hydroxy-3-(*R*)-(*n*-butyl)-3-[2-(*S*)-((3,4-dichlorophenyl)amino-carbonyl)-pyrrolidin-1-carbonyl]-2-(*S*)-hydroxypropionamide



The title compound was prepared according to General Procedure F from 3,4-dichloroaniline. ^{1}H NMR ($CDCl_3$): δ 7.94-7.44 (m, 3H), 4.73-4.71 (d, J = 8.24 Hz, 1H), 4.52-4.51 (d, J = 2.8 Hz, 1H), 3.95-3.94 (m, 2H), 3.49 (t, J =5.8 & 6.0 Hz, 1H), 2.52-1.99 (m, 6H), 1.70-1.57 (m, 4H), 1.122 (t, J = 6.9 & 7.1 Hz, 3H). ES-MS: calcd. For $C_{19}H_{25}Cl_2N_3O_5$ (445.1); found: 446.3 [M+1].

Example 119

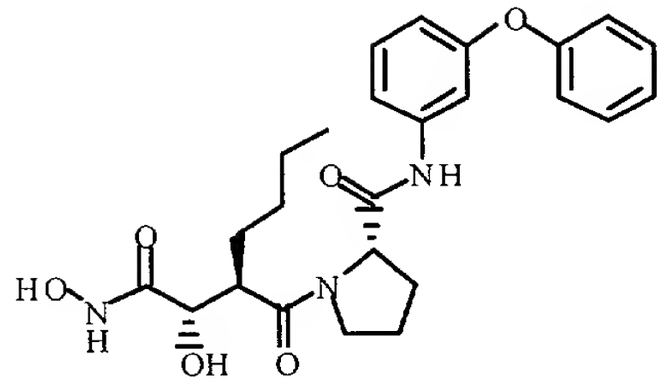
Synthesis of *N*-hydroxy-3-(*R*)-(*n*-butyl)-3-[2-(*S*)-((5-methylisoxazol-3-yl)amino-carbonyl)pyrrolidin-1-carbonyl]-2-(*S*)-hydroxypropionamide



The title compound was prepared according to General Procedure F from 3-amino-5-methylisoxazole. ^{1}H NMR (DMSO-d6): δ 6.64-5.95 (m, 1H), 4.66-4.62 (dd, J = 4.9 & 4.7 Hz, 1H), 4.01-3.93 (m, 1H), 3.76-3.70 (m, 1H), 3.56 (bs, 3H), 3.11-3.05 (t, J = 8.8, 1H), 2.70-2.00 (m, 6H), 1.59-1.37 (m, 4H), 1.02 (t, J = 5.8 & 7.1 Hz, 3H). ES-MS: calcd. For $C_{17}H_{26}N_4O_6$ (382.42); found: 383.3 [M+1].

Example 120

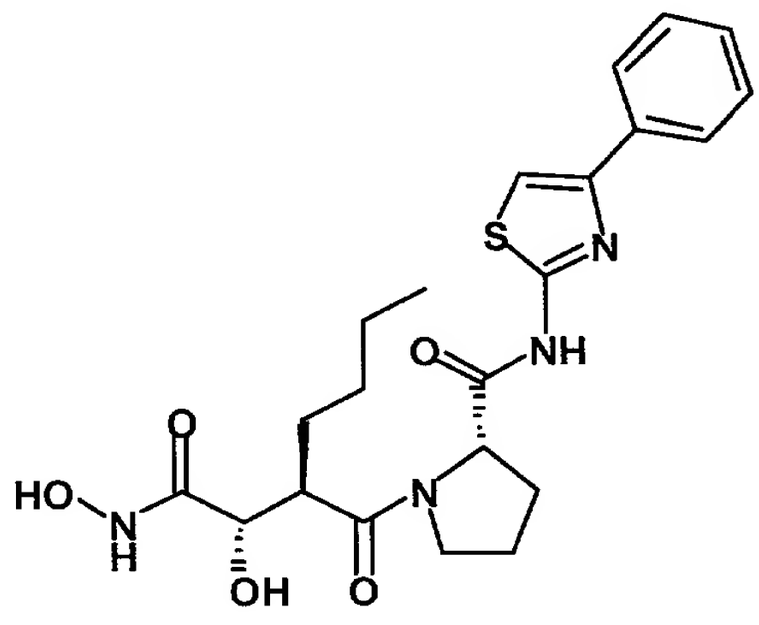
Synthesis of *N*-hydroxy-3-(*R*)-(*n*-butyl)-3-[2-(*S*)-((3-phenoxyphenyl)aminocarbonyl)-pyrrolidin-1-carbonyl]-2-(*S*)-hydroxypropionamide



The title compound was prepared according to General Procedure F from 3-phenyoxyaniline. ^{1}H NMR ($CDCl_3$): δ 7.55-6.88 (m, 9H), 4.75-4.72 (d, J = 7.7 Hz, 1H), 4.47 (bs, 1H), 3.90-3.88 (m, 2H), 3.46-3.44 (m, 1H), 2.51-1.96 (m, 6H), 1.65-1.53 (m, 4H), 1.09 (t, J = 6.7 & 7.1 Hz, 3H). ES-MS: calcd. For $C_{25}H_{31}N_3O_6$ (469.54); found: 470.4 [M+1].

Example 121

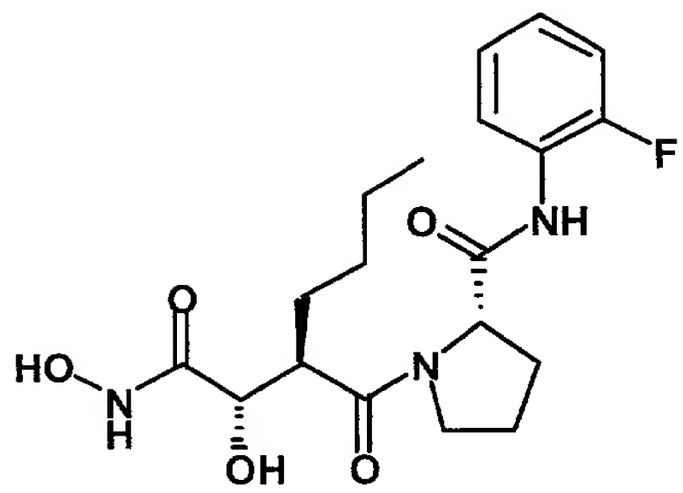
Synthesis of *N*-hydroxy-3-(*R*)-(*n*-butyl)-3-[2-(*S*)-((4-phenylthiazol-2-yl)amino-carbonyl)-pyrrolidin-1-carbonyl]-2-(*S*)-hydroxypropionamide



The title compound was prepared according to General Procedure F from 2-amino-5-phenylthiazole. ^{1}H NMR ($CDCl_3$): δ 7.94-7.28 (m, 6H), 4.89-4.88 (d, J = 4.4 Hz, 1H), 4.47-4.47 (d, J = 2.5 Hz, 1H), 3.92-4.05 (m, 2H), 3.48-3.44 (m, 1H), 2.54-1.95 (m, 6H), 1.57-1.48 (m, 4H), 1.10 (t, J = 6.6 & 7.7 Hz, 3H). ES-MS: calcd. For $C_{22}H_{28}N_4O_5S$ (460.55); found: 461.2 [M+1].

Example 122

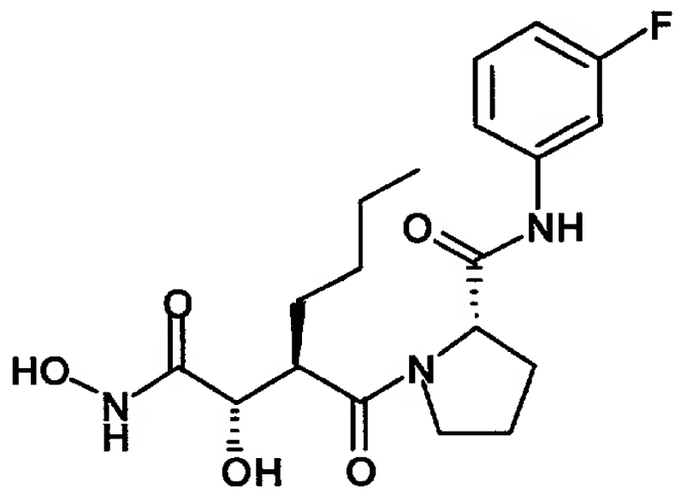
Synthesis of *N*-hydroxy-3-(*R*)-(*n*-butyl)-3-[2-(*S*)-((2-fluorophenyl)aminocarbonyl)-pyrrolidin-1-carbonyl]-2-(*S*)-hydroxypropionamide



The title compound was prepared according to General Procedure F from 2-fluoroaniline. ^{1}H NMR ($CDCl_3$): δ 8.42-7.23 (m, 4H), 4.97-4.95 (d, J = 6.9 Hz, 1H), 4.49 (bs, 1H), 3.96-3.83 (m, 2H), 3.49 (t, J = 5.5 & 7.4 Hz, 1H), 2.61-2.01 (m, 6H), 1.64-1.46 (m, 4H), 1.06 (t, J = 6.6 & 7.1 Hz, 3H). ES-MS: calcd. For $C_{19}H_{26}FN_3O_5$ (395.43); found: 396.4 [M+1].

Example 123

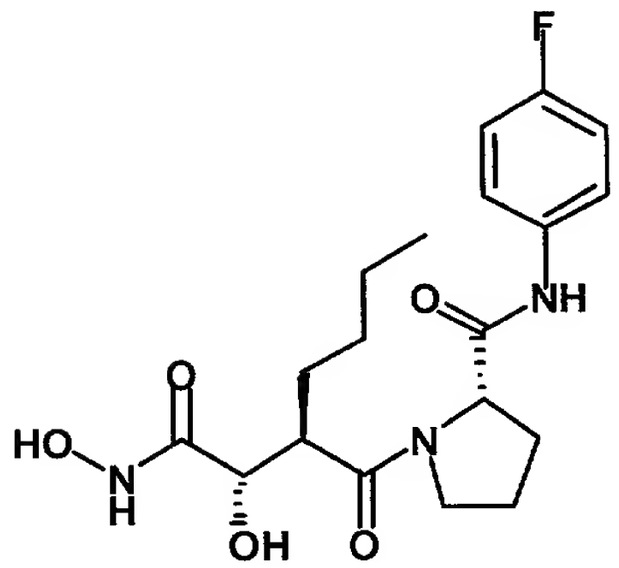
Synthesis of *N*-hydroxy-3-(*R*)-(*n*-butyl)-3-[2-(*S*)-((3-fluorophenyl)aminocarbonyl)-pyrrolidin-1-carbonyl]-2-(*S*)-hydroxypropionamide



The title compound was prepared according to General Procedure F from 3-fluoroaniline. ^{1}H NMR ($CDCl_3$): δ 7.66-6.92 (m, 4H), 4.75-4.73 (d, J = 8.0 Hz, 1H), 4.52 (bs, 1H), 3.94 (t, J = 8.5 & 8.81 Hz, 2H), 3.49 (bs, 1H), 2.57-1.99 (m, 6H), 1.70-1.56 (m, 4H), 1.12 (t, J = 6.6 & 6.9 Hz, 3H). ES-MS: calcd. For $C_{19}H_{26}FN_3O_5$ (395.43); found: 396.3 [M+1].

Example 124

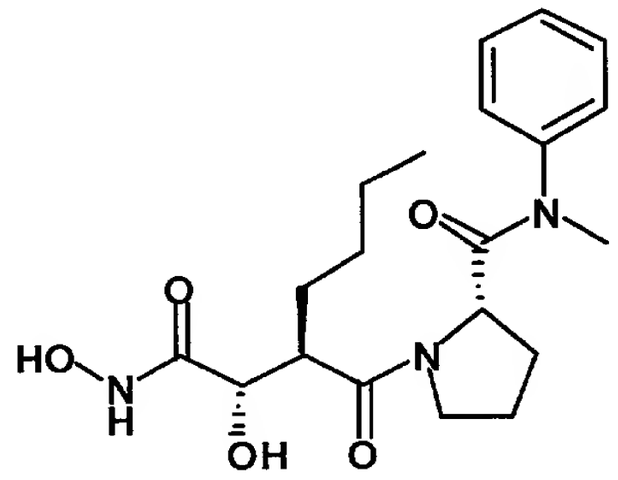
Synthesis of *N*-hydroxy-3-(*R*)-(*n*-butyl)-3-[2-(*S*)-((4-fluorophenyl)aminocarbonyl)-pyrrolidin-1-carbonyl]-2-(*S*)-hydroxypropionamide



The title compound was prepared according to General Procedure F from 4-fluoroaniline. ^{1}H NMR ($CDCl_3$): δ 7.71-7.13 (m, 4H), 4.74-4.71 (d, J = 8.2 Hz, 1H), 4.51-4.49 (d, J = 2.8 Hz, 1H), 3.96-3.90 (m, 2H), 3.52-3.46 (m, 1H), 2.58-1.96 (m, 6H), 1.69-1.54 (m, 4H), 1.11 (t, J = 6.9 Hz, 3H). ES-MS: calcd. For $C_{19}H_{26}FN_3O_5$ (395.43); found: 396.3 [M+1].

Example 125

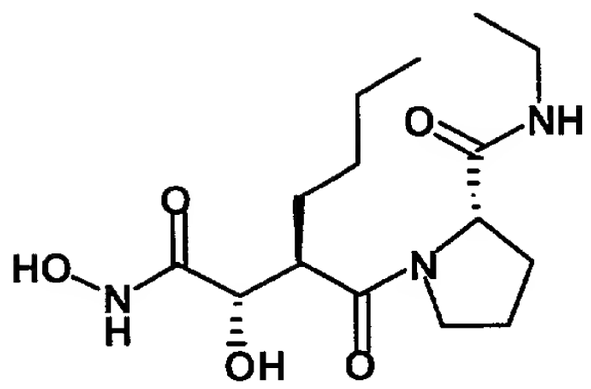
Synthesis of *N*-hydroxy-3-(*R*)-(*n*-butyl)-3-[2-(*S*)-((*N*-phenyl-*N*-methylamino)-carbonyl)pyrrolidin-1-carbonyl]-2-(*S*)-hydroxypropionamide



The title compound was prepared according to General Procedure F from N-methylaniline. ^{1}H NMR ($CDCl_3$): δ 7.26-7.5 (m, 5H), 4.38 (d, J = 7.1 Hz, 1H), 4.24 (bs, 1H), 3.69-3.65 (m, 5H), 3.33-3.20 (m, 1H), 2.08-1.82 (m, 6H), 1.49-1.36 (m, 4H), 0.94 (t, J = 7.1 Hz, 3H). ES-MS: calcd. For $C_{20}H_{29}N_3O_5$ (391.47); found: 392.4 [M+1].

Example 126

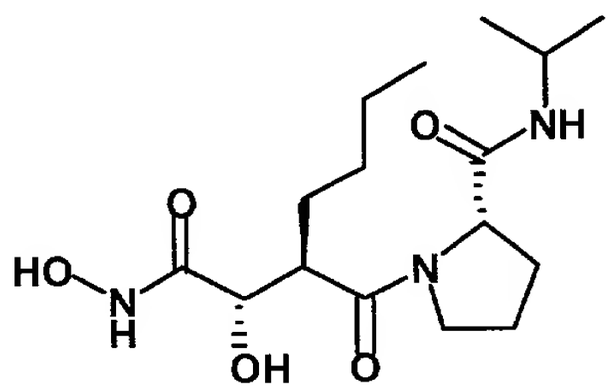
Synthesis of *N*-hydroxy-3-(*R*)-(*n*-butyl)-3-[2-(*S*)-((ethyl)aminocarbonyl)-pyrrolidin-1-carbonyl]-2-(*S*)-hydroxypropionamide



The title compound was prepared according to General Procedure F from ethylamine. ^{1}H NMR ($CDCl_3$): δ 4.39-4.37 (d, J = 6.0 Hz, 1H), 4.25-4.24 (d, J = 2.5 Hz, 1H), 3.69-3.52 (m, 4H), 3.20-3.32 (m, 1H), 2.25-1.76 (m, 6H), 1.44-1.25 (m, 4H), 1.183-1.11 (m, 3H), 0.94-0.85 (m, 3H). ES-MS: calcd. For $C_{15}H_{27}N_3O_5$ (329.4); found: 330.4 [M+1].

Example 127

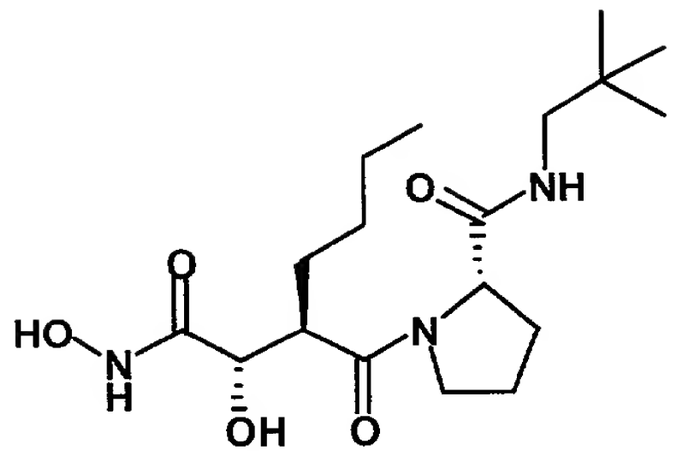
Synthesis of *N*-hydroxy-3-(*R*)-(*n*-butyl)-3-[2-(*S*)-((2-propyl)aminocarbonyl)-pyrrolidin-1-carbonyl]-2-(*S*)-hydroxypropionamide



The title compound was prepared according to General Procedure F from 2-aminopropane. ^{1}H NMR ($CDCl_3$): δ 4.41-4.38 (d, J = 8.0 Hz, 1H), 4.26-4.25 (d, J = 2.2 Hz, 1H), 4.01-3.94 (dd, J = 6.6 Hz, 1H), 3.66 (t, J = 7.4 Hz, 2H), 3.25-3.22 (m, 1H), 2.21-1.77 (m, 6H), 1.44-1.22 (m, 4H), 1.19-1.11 (m, 6H). 0.893 (t, J = 6.6 Hz, 3H). ES-MS: calcd. For $C_{16}H_{29}N_3O_5$ (343.42); found: 344.4 [M+1].

Example 128

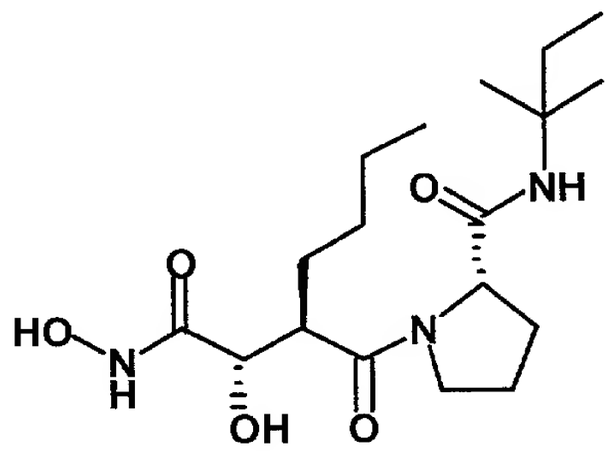
Synthesis of *N*-hydroxy-3-(*R*)-(*n*-butyl)-3-[2-(*S*)-((2,2-dimethylpropyl)-aminocarbonyl)pyrrolidin-1-carbonyl]-2-(*S*)-hydroxypropionamide



The title compound was prepared according to General Procedure F from 2,2-dimethylpropylamine. ^{1}H NMR ($CDCl_3$): δ 4.52-4.5 (d, J = 6.0 Hz, 1H), 4.26-4.25 (d, J = 2.5 Hz, 1H), 3.7-3.59 (m, 2H), 3.28-3.22 (m, 1H), 3.12-2.94 (m. 2H), 2.29-1.73 (m, 6H), 1.44-1.33 (m, 4H), 0.93-0.88 (m, 12H). ES-MS: calcd. For $C_{18}H_{33}N_3O_5$ (371.48); found: 372.4 [M+1].

Example 129

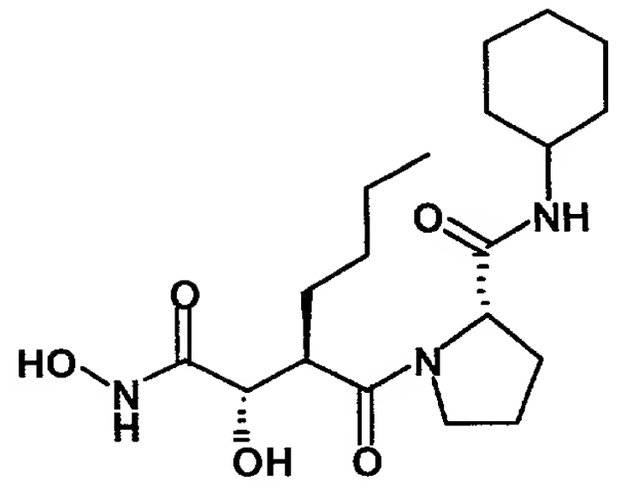
Synthesis of *N*-hydroxy-3-(*R*)-(*n*-butyl)-3-[2-(*S*)-((1,1-dimethylpropyl)-aminocarbonyl)-pyrrolidin-1-carbonyl]-2-(*S*)-hydroxypropionamide



The title compound was prepared according to General Procedure F from 1,1-dimethylpropylamine. ^{1}H NMR ($CDCl_3$): δ 4.42-4.40 (d, J = 7.7 Hz, 1H), 4.26 (bs, 1H), 3.67-3.61 (m, 2H), 3.26-3.22 (t, J = 5.0 & 7.1 Hz, 1H), 2.22-1.65 (m, 6H), 1.44-1.24 (m, 6H), 0.94-0.79 (m, 6H). ES-MS: calcd. For $C_{18}H_{33}N_3O_5$ (371.48); found: 372.4 [M+1].

Example 130

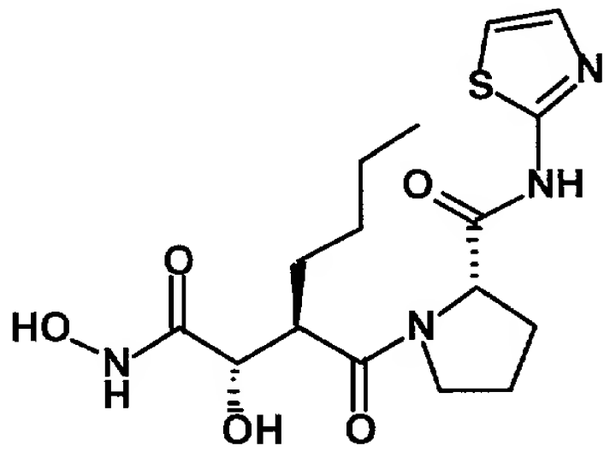
Synthesis of *N*-hydroxy-3-(*R*)-(*n*-butyl)-3-[2-(*S*)-((cyclohexyl)aminocarbonyl)-pyrrolidin-1-carbonyl]-2-(*S*)-hydroxypropionamide



The title compound was prepared according to General Procedure F from cyclohexylamine. ^{1}H NMR ($CDCl_3$): δ 4.43-4.40 (d, J = 8.0 Hz, 1H), 4.26-4.25 (d, J = 2.5 Hz, 1H), 3.66-3.63 (d, J = 7.4 Hz, 3H), 3.27-3.21 (m, 1H), 2.21-1.10 (m, 20H), 0.94-0.89 (m, 3H). ES-MS: calcd. For $C_{19}H_{33}N_3O_5$ (383.49); found: 384.3 [M+1].

Example 131

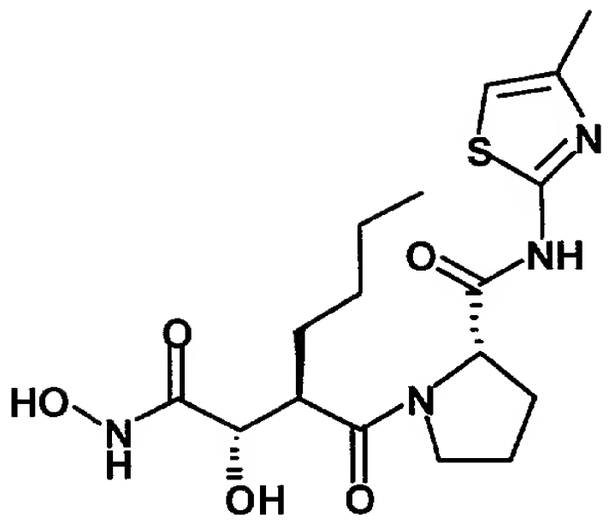
Synthesis of *N*-hydroxy-3-(*R*)-(*n*-butyl)-3-[2-(*S*)-((thiazol-2-yl)aminocarbonyl)-pyrrolidin-1-carbonyl]-2-(*S*)-hydroxypropionamide



The title compound was prepared according to General Procedure F from 2-aminothiazole. ^{1}H NMR ($CDCl_3$): δ 7.5-7.04 (m, 2H), 4.66 (t, J = 5.0 Hz, 1H), 4.27-4.26 (d, J = 2.5 Hz, 1H), 3.86-3.76 (m, 2H), 3.3-3.25 (m, 1H), 2.34-1.74 (m, 6H), 1.36-1.28 (m, 4H), 0.93-0.86 (m, 3H). ES-MS: calcd. For $C_{16}H_{24}N_4O_5S$ (384.46); found: 385.2 [M+1].

Example 132

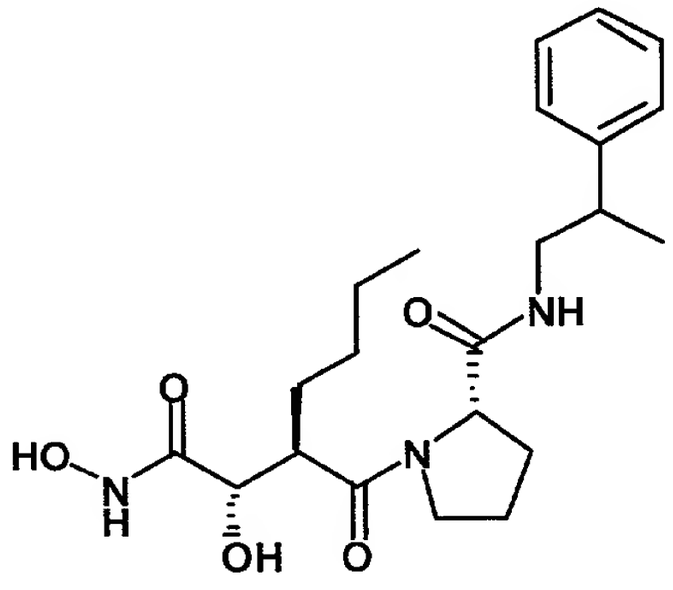
Synthesis of *N*-hydroxy-3-(*R*)-(*n*-butyl)-3-[2-(*S*)-((4-methylthiazol-2-yl)amino-carbonyl)pyrrolidin-1-carbonyl]-2-(*S*)-hydroxypropionamide



The title compound was prepared according to General Procedure F from 2-amino-4-methylthiazole. ^{1}H NMR ($CDCl_3$): δ 6.62-6.61(d, J = 1.1 Hz, 1H), 4.65-4.63 (dd, J = 4.7 & 5.2 Hz, 1H), 4.26-4.25 (d, J = 2.5 Hz, 1H), 3.85-3.78 (dd, J = 6.0 & 7.4 Hz, 2H), 3.29-3.25 (dd, J = 5.2 & 5.0 Hz, 1H), 2.46-1.69 (m, 9H), 1.38-1.27 (m, 4H), 0.893-0.85 (m, 3H). ES-MS: calcd. For $C_{17}H_{26}N_4O_5S$ (398.48); found: 399.3 [M+1].

Example 133

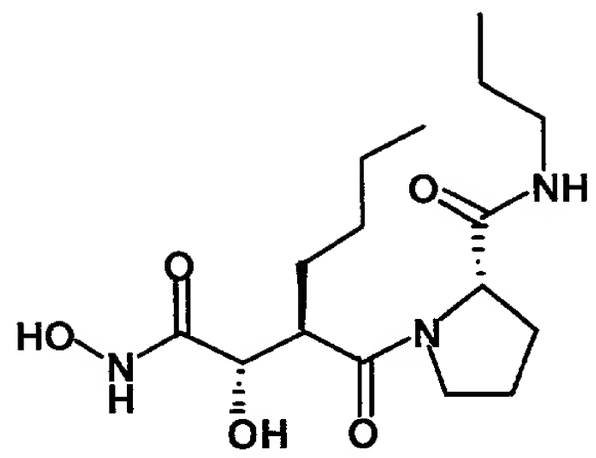
Synthesis of *N*-hydroxy-3-(*R*)-(*n*-butyl)-3-[2-(*S*)-((2-phenylpropyl)aminocarbonyl)-pyrrolidin-1-carbonyl]-2-(*S*)-hydroxypropionamide



The title compound was prepared according to General Procedure F from 1-amino-2-phenylpropane. ^{1}H NMR ($CDCl_3$): δ 7.3-6.78 (m, 5H), 5.17 (bs, 1H), 4.34 (bs, 1H), 4.21 (bs, 1H), 3.61-3.16 (m, 4H), 3.25-3.22 (m, 1H), 2.92 (bs, 1H), 2.09-1.09 (m, 13H), 0.94-0.83 (m, 3H). ES-MS: calcd. For $C_{22}H_{33}N_3O_5$ (419.52); found: 420.3 [M+1].

Example 134

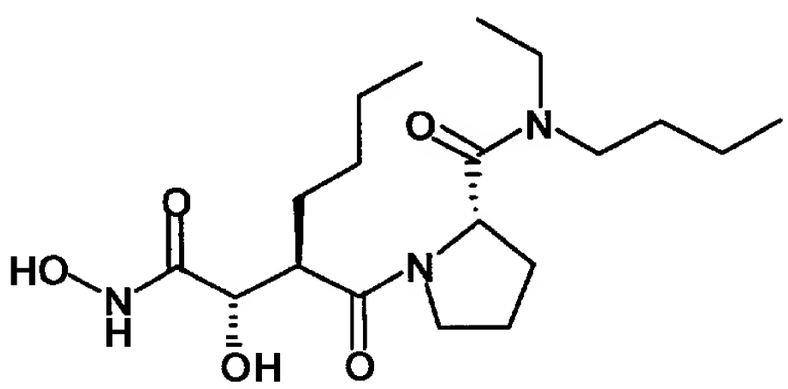
Synthesis of *N*-hydroxy-3-(*R*)-(*n*-butyl)-3-[2-(*S*)-((*n*-propyl)aminocarbonyl)-pyrrolidin-1-carbonyl]-2-(*S*)-hydroxypropionamide



The title compound was prepared according to General Procedure F from propylamine. ^{1}H NMR ($CDCl_3$): δ 4.44-4.41 (d, J = 7.4 Hz, 1H), 4.25 (bs, 1H), 3.67-3.65 (d, J = 5.5 Hz, 2H), 3.24-3.14 (m, 3H), 2.23-1.79 (m, 6H), 1.54-1.35 (m, 6H), 0.94-0.85 (m, 6H). ES-MS: calcd. For $C_{16}H_{29}N_3O_5$ (343.42); found: 344.4 [M+1].

Example 135

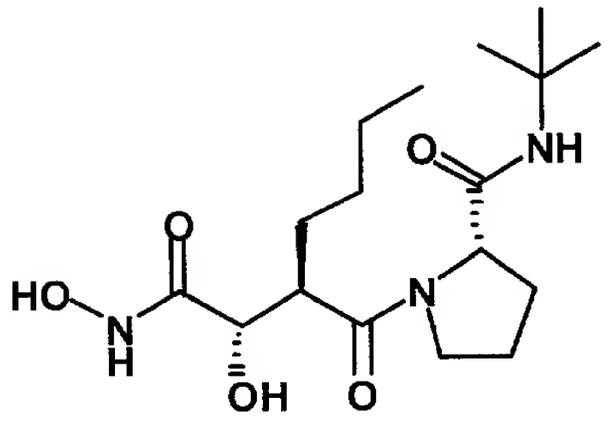
Synthesis of *N*-hydroxy-3-(*R*)-(*n*-butyl)-3-[2-(*S*)-((*N*-butyl-*N*-methylamino)carbonyl)-pyrrolidin-1-carbonyl]-2-(*S*)-hydroxypropionamide



The title compound was prepared according to General Procedure F from *N*-ethyl-*n*-butylamine. ^{1}H NMR ($CDCl_3$): δ 4.74 (t, J = 3.9 Hz, 1H), 4.25 (bs, 1H), 3.73-3.02 (m, 7H), 2.16-1.74 (m, 6H), 1.53-1.23 (m, 8H), 1.08 (t, J = 6.9 & 7.1 Hz, 2H), 0.98-0.88 (m, 9H). ES-MS: calcd. For $C_{19}H_{35}N_3O_5$ (358.50); found: 386.4 [M+1].

Example 136

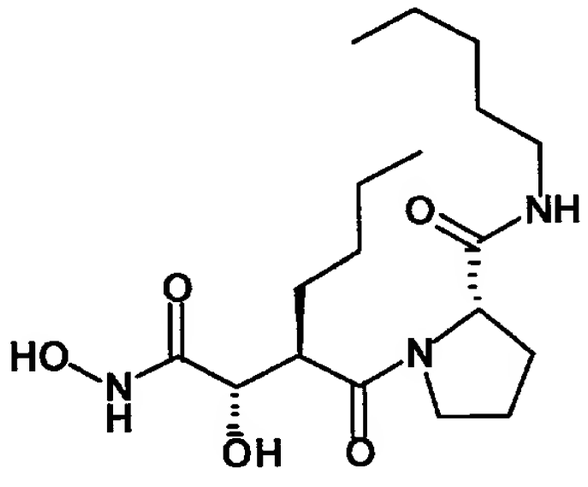
Synthesis of *N*-hydroxy-3-(*R*)-(*n*-butyl)-3-[2-(*S*)-((*tert*-butyl)aminocarbonyl)-pyrrolidin-1-carbonyl]-2-(*S*)-hydroxypropionamide



The title compound was prepared according to General Procedure F from *t*-butylamine. ^{1}H NMR ($CDCl_3$): δ 4.36-4.34 (d, J = 6.7 Hz, 1H), 4.31-4.25 (d, J = 6.5 Hz, 1H), 3.65-3.55 (m, 2H), 3.26-3.22 (m, 1H), 2.2-1.8 (m, 6H), 1.5-1.3 (m, 13H), 0.94-0.85 (m, 3H). ES-MS: calcd. For $C_{17}H_{31}N_3O_5$ (357.45); found: 358.4 [M+1].

Example 137

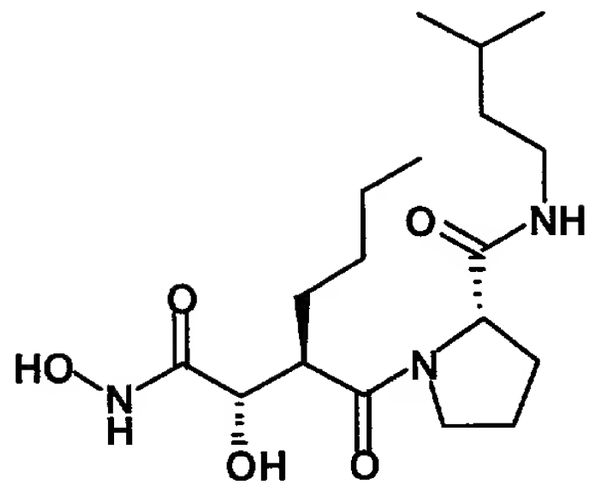
Synthesis of *N*-hydroxy-3-(*R*)-(*n*-butyl)-3-[2-(*S*)-((*n*-pentyl)aminocarbonyl)-pyrrolidin-1-carbonyl]-2-(*S*)-hydroxypropionamide



The title compound was prepared according to General Procedure F from *n*-pentylamine. ^{1}H NMR ($CDCl_3$): δ 4.44-4.41 (d, J = 7.4 Hz, 1H), 4.24 (d, J = 2.2 Hz, 1H), 3.71-3.62 (m, 2H), 3.27-3.15 (m, 3H), 2.26-1.74 (m, 6H), 1.52-1.24 (m, 10H), 0.94-0.86 (m, 6H). ES-MS: calcd. For $C_{18}H_{33}N_3O_5$ (371.48); found: 372.4 [M+1].

Example 138

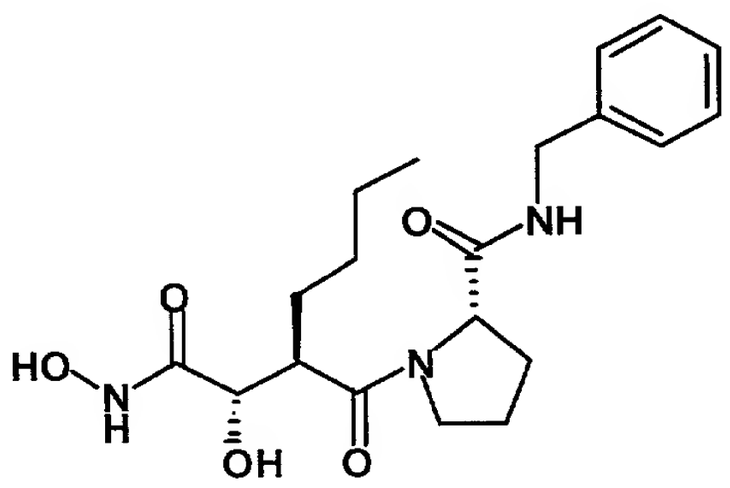
Synthesis of *N*-hydroxy-3-(*R*)-(*n*-butyl)-3-[2-(*S*)-((3-methylbutyl)aminocarbonyl)-pyrrolidin-1-carbonyl]-2-(*S*)-hydroxypropionamide



The title compound was prepared according to General Procedure F from 3-methyl-1-butylamine. ^{1}H NMR ($CDCl_3$): δ 4.44-4.41 (d, J = 7.4 Hz, 1H), 4.25-4.24 (d, J = 2.5 Hz, 1H), 3.71-3.61 (m, 2H), 3.27-3.17 (m, 3H), 2.64-1.77 (m, 6H), 1.63-1.33 (m, 7H), 0.94-0.88 (m, 9H). ES-MS: calcd. For $C_{18}H_3N_3O_5$ (271.48); found: 372.5 [M+1].

Example 139

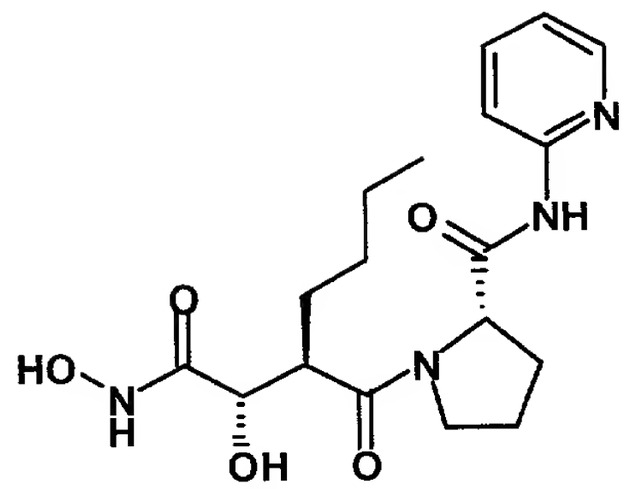
Synthesis of *N*-hydroxy-3-(*R*)-(*n*-butyl)-3-[2-(*S*)-((benzyl)aminocarbonyl)pyrrolidin-1-carbonyl]-2-(*S*)-hydroxypropionamide



The title compound was prepared according to General Procedure F from benzylamine. ^{1}H NMR ($CDCl_3$): δ 7.37-7.21 (m, 5H), 4.49-4.29 (m, 3H), 4.20-4.19 (d, J = 2.5 Hz 1H), 3.71-3.62 (m, 2H), 3.19 (t, J = 7.4 & 5.5 Hz, 1H), 2.22-1.73 (m, 6H), 1.32-1.29 (m, 4H), 0.88 (t, J = 6.6 & 6.9 Hz, 3H). ES-MS: calcd. For $C_{20}H_{29}N_3O_5$ (391.47); found: 392.4 [M+1].

Example 140

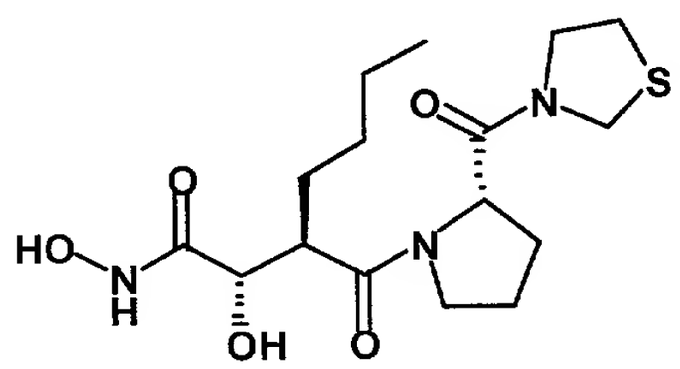
Synthesis of *N*-hydroxy-3-(*R*)-(*n*-butyl)-3-[2-(*S*)-((pyridin-2-yl)aminocarbonyl)-pyrrolidin-1-carbonyl]-2-(*S*)-hydroxypropionamide



The title compound was prepared according to General Procedure F from 2-aminopyridine. ^{1}H NMR ($CDCl_3$): δ 8.4-7.47 (m, 4H), 4.87-4.83 (m, 1H), 4.47-4.46 (d, J = 2.8 Hz, 1H), 4.04-3.87 (m, 2H), 3.5-3.48 (t, J = 2.8 & 4.9 Hz, 1H), 2.52-1.95 (m, 6H), 1.63-1.56 (m, 4H), 1.11 (t, J = 7.1 Hz, 3H). ES-MS: calcd. For $C_{18}H_{26}N_4O_5$ (378.43); found: 377.2 [M-1].

Example 141

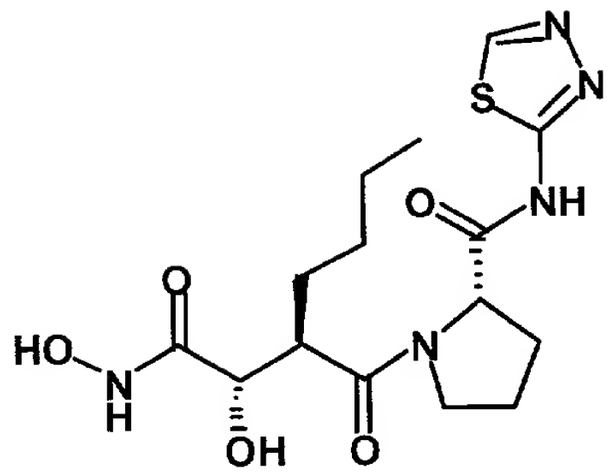
Synthesis of *N*-hydroxy-3-(*R*)-(*n*-butyl)-3-[2-(*S*)-((thiazolidin-1-yl)aminocarbonyl)-pyrrolidin-1-carbonyl]-2-(*S*)-hydroxypropionamide



The title compound was prepared according to General Procedure F from thiazolidine. ^{1}H NMR ($CDCl_3$): δ 4.94-4.66 (m, 3H), 4.46-4.45(d, J = 2.2 Hz, 1H), 4.24-3.84 (m, 4H), 3.46-3.18 (m, 3H), 2.37-2.01 (m, 6H), 1.68-1.53 (m, 4H), 1.12 (t, J = 7.417 & 6.767 Hz, 3H). ES-MS: calcd. For $C_{16}H_{27}N_3O_5S$ (373.47); found: 374.6 [M+1].

Example 142

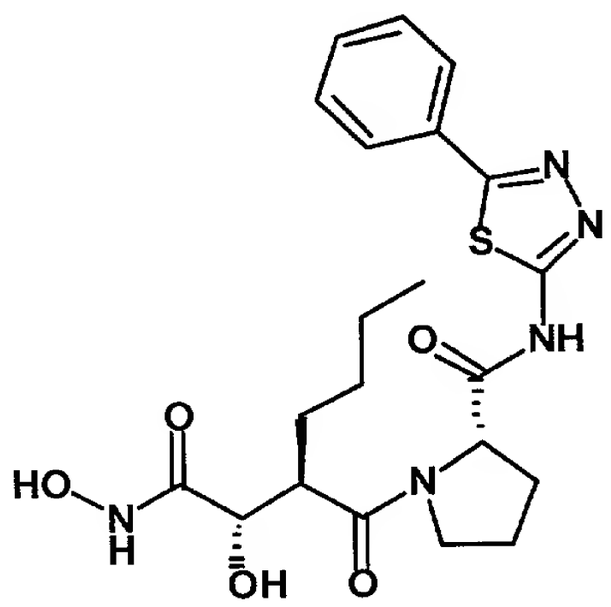
Synthesis of *N*-hydroxy-3-(*R*)-(*n*-butyl)-3-[2-(*S*)-((thiadiazolidin-5-yl)amino-carbonyl)pyrrolidin-1-carbonyl]-2-(*S*)-hydroxypropionamide



The title compound was prepared according to General Procedure F from 2-aminothiadiazole. ^{1}H NMR ($CDCl_3$): δ 7.47-7.46 (d, J = 5.5 Hz, 1H), 5.03-5.02 (d, J = 5.5 Hz, 1H), 4.49-4.47 (d, J = 3.4 Hz, 1H), 4-3.89 (m, 2H), 3.45-3.44 (d, J = 3.6 Hz, 1H), 2.4-1.9 (m, 6H), 1.53 (bs, 4H), 1.08 (t, J = 6.6 & 6.9 Hz, 3H). ES-MS: calcd. For $C_{15}H_{23}N_5O_5S$ (385.44); found: 386.5 [M+1].

Example 143

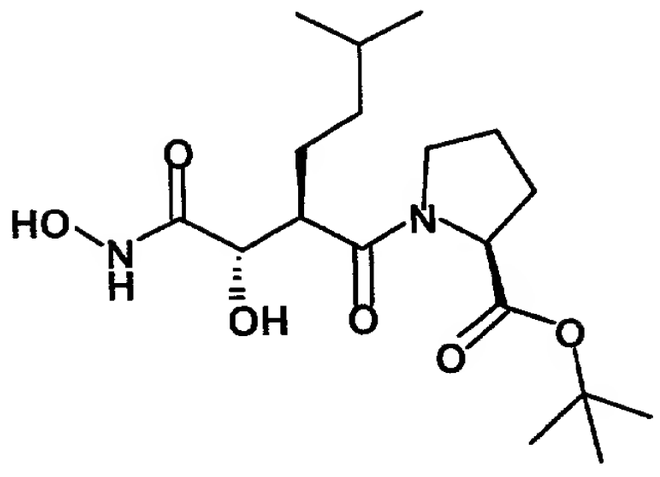
Synthesis of *N*-hydroxy-3-(*R*)-(*n*-butyl)-3-[2-(*S*)-((5-phenylthiadiazolidin-2-yl)-aminocarbonyl)-pyrrolidin-1-carbonyl]-2-(*S*)-hydroxypropionamide



The title compound was prepared according to General Procedure F from 2-amino-5-phenylthiadiazole. ^{1}H NMR ($CDCl_3$): δ 7.82-7.21 (m, 5H), 4.82-4.79 (d, J = 7.4 Hz, 1H), 4.24-4.23 (d, J = 3.6 Hz, 1H), 3.76-3.62 (m, 2H), 3.20-3.19 (d, J = 3.6 Hz, 1H), 2.18-1.95 (m, 6H), 1.68-1.66 (m, 4H), 0.807 (t, J = 6.6 & 7.2 Hz, 3H). ES-MS: calcd. For $C_{21}H_{27}N_5O_5S$ (461.54); found: 462.7 [M+1].

Example 144

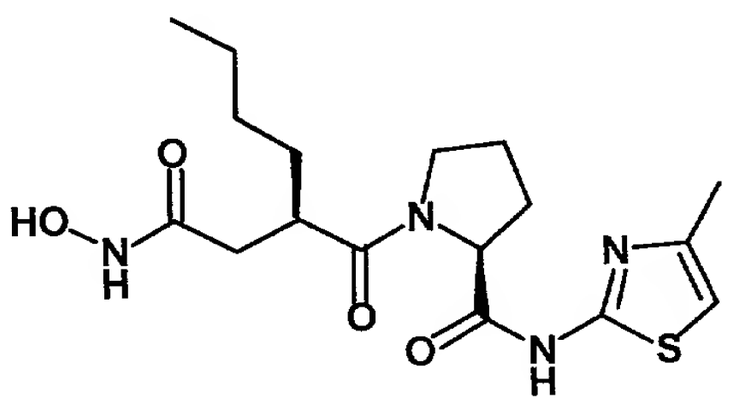
Synthesis of *N*-hydroxy-3-(*R*)-(*n*-3-methylbutyl)-3-[2-(*S*)-(*tert*-butoxycarbonyl)-pyrrolidin-1-carbonyl]-2-(*S*)-hydroxypropionamide



The title compound was prepared according to General Procedure F from 3-methyl-1-bromo-2-butene and proline –O-t-butyl ester. ^{1}H NMR ($CDCl_3$): δ 4.52 (t, J = 4.4 Hz, 1H), 4.46 (t, J = 1.3 & 2.2 Hz, 1H), 3.93-3.76 (m, 1H), 3.4-3.34 (m, 2H), 2.41-1.95 (m, 6H), 1.81-1.49 (m, 12H), 1.10 (t, J = 6.6 & 6.9 Hz, 6H). ES-MS: calcd. For $C_{18}H_{32}N_2O_6$ (372.46); found: 373.5 [M+1].

Example 145

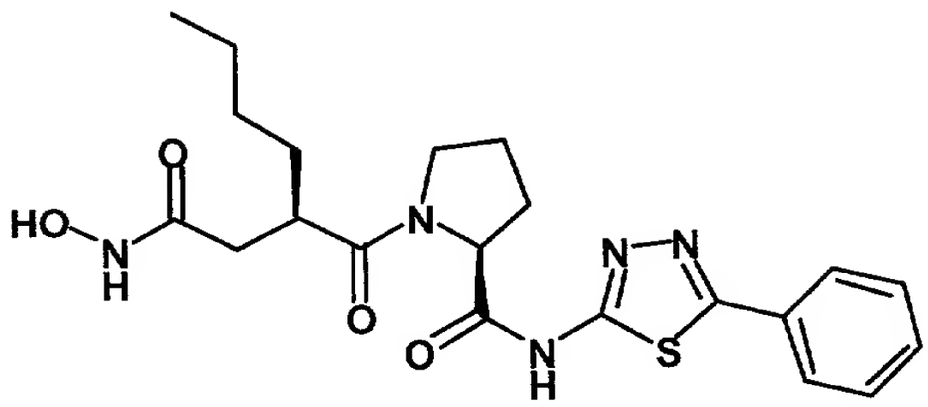
Synthesis of *N*-hydroxy-3-(*R*)-(*n*-butyl)-3-[2-(*S*)-((4-methylthiazol-2-yl)amino-carbonyl)pyrrolidin-1-carbonyl]propionamide



The title compound was prepared according to General Procedure E from 2-amino-4-methylthiazole. ^{1}H NMR (DMSO-d6): δ 6.74 (s, 1H), 4.48 (dd, 8.5 & 4.7 Hz, 1H), 3.75-3.63 (m, 1H), 3.61-3.55 (m, 1H), 2.95 (bs, 1H), 2.25 (s, 3H), 2.23-1.80 (m, 6H), 1.45-1.25 (m, 6H), 0.85 (t, 6.6 Hz, 3H). ES-MS: cald. For $C_{17}H_{26}N_4O_4S$ (382.17); found 383.6 [M+1].

Example 146

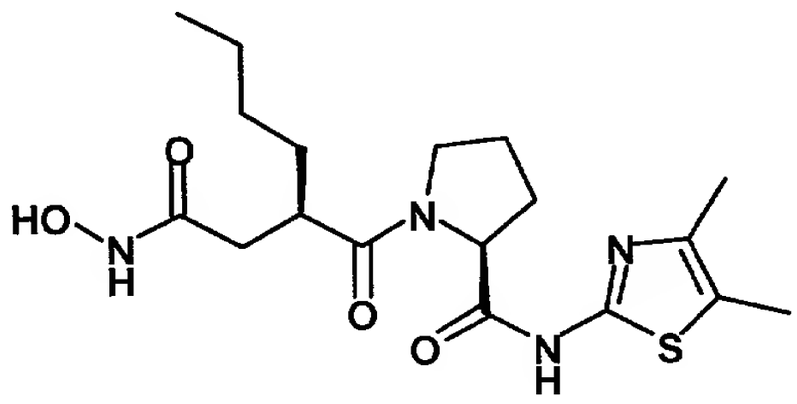
Synthesis of *N*-hydroxy-3-(*R*)-(*n*-butyl)-3-[2-(*S*)-((5-phenylthiadiazol-2-yl)amino-carbonyl)pyrrolidin-1-carbonyl]propionamide



The title compound was prepared according to General Procedure E from 2-amino-5-phenylthiadiazole. ^{1}H NMR (DMSO-d6): δ10.3 (s, 1H), 7.94 (m, 2H), 7.53 (m, 3H), 4.56 (dd, 8.5 & 4.8 Hz, 1H), 3.8-3.59 (m, 2H), 2.96 (bs, 1H), 2.29-1.86 (m, 6H), 1.45-1.27 (m, 6H), 0.87 (t, 6.6 Hz, 3H). ES-MS: cald. For $C_{21}H_{27}N_5O_4S$ (445.18); found 446.5 [M+1].

Example 147

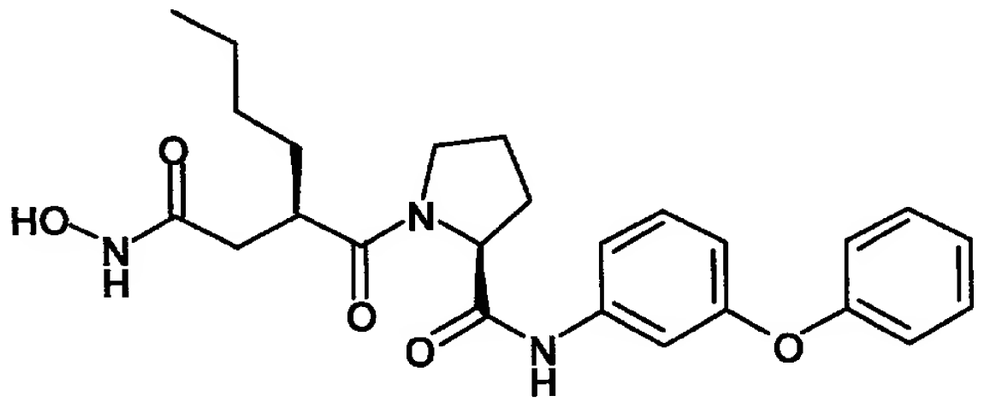
Synthesis of *N*-hydroxy-3-(*R*)-(*n*-butyl)-3-[2-(*S*)-((4,5-dimethylthiazol-2-yl)amino-carbonyl)pyrrolidin-1-carbonyl]propionamide



The title compound was prepared according to General Procedure E from 2-amino-4,5-dimethylthiazole. ^{1}H NMR (DMSO-d6): δ 4.45 (dd, 8.2 & 4.8 Hz, 1H), 3.74-3.62 (m, 1H), 3.60-3.55 (m, 1H), 2.93 (bs, 1H), 2.22 (s, 3H), 2.15 (s, 3H), 2.11-1.78 (m, 6H), 1.46-1.25 (m, 6H), 0.85 (t, 6.3 Hz, 3 H). ES-MS: cald. For $C_{18}H_{28}N_4O_4S$ (396.18); found 397.5 [M+1].

Example 148

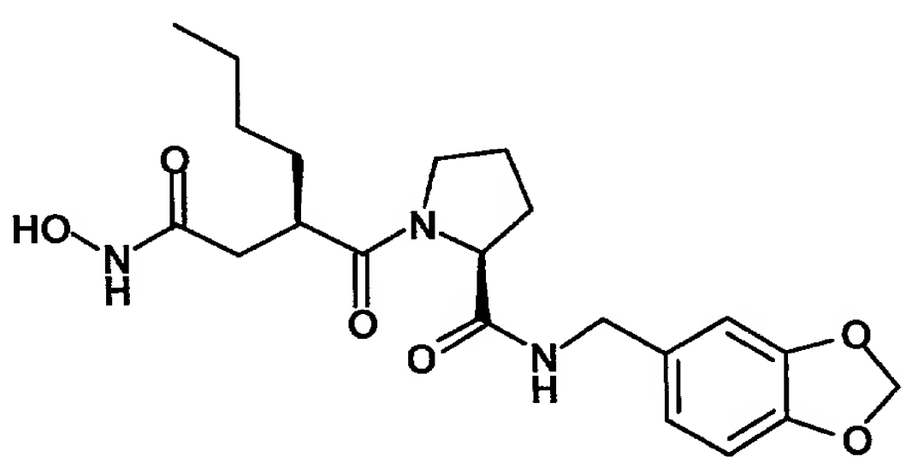
Synthesis of *N*-hydroxy-3-(*R*)-(*n*-butyl)-3-[2-(*S*)-((3-phenoxyphenyl)amino-carbonyl)pyrrolidin-1-carbonyl]propionamide



The title compound was prepared according to General Procedure E from 3-phenoxyaniline. ^{1}H NMR (DMSO-d6): δ 7.42 (m, 2H), 7.37 (m, 3H), 7.15 (m, 1H), 7.02 (m, 2H), 6.69 (m, 1H), 4.35 (dd, 8.0 & 4.5 Hz, 1H), 3.71-3.45 (m, 2H), 2.93 (bs, 1H), 2.28-1.82 (m, 6H), 1.42-1.22 (m, 6H), 0.82 (t, 6.3 Hz, 3H). ES-MS: cald. For $C_{25}H_{31}N_3O_5$ (453.23); found 454.5 [M+1].

Example 149

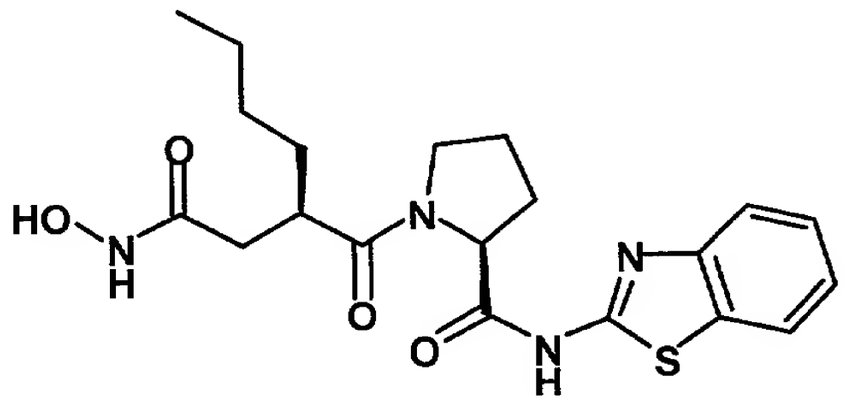
Synthesis of *N*-hydroxy-3-(*R*)-(*n*-butyl)-3-[2-(*S*)-((3,4-methylenedioxybenzyl)amino-carbonyl)pyrrolidin-1-carbonyl]propionamide



The title compound was prepared according to General Procedure E from piperonylamine. ^{1}H NMR (DMSO-d6): δ 10.4 (bs, 1H), 8.18 (m, 1H), 6.87-6.69 (m, 3H), 6.00-5.96 (m, 2H), 4.29-4.11 (m, 2H), 3.71-3.53 (m, 2H), 2.92 (bs, 1H), 2.29-1.76 (m, 6H), 1.49-1.21 (m, 6H), 0.84 (m, 3H). ES-MS: cald. For $C_{21}H_{29}N_3O_6$ (419.21); found 420.5 [M+1].

Example 150

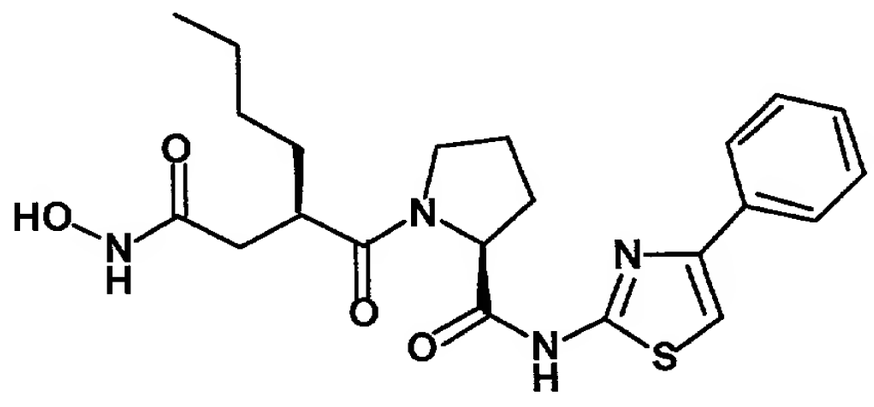
Synthesis of *N*-hydroxy-3-(*S*)-(*n*-butyl)-3-[2-(*S*)-((benzthiazol-2-yl)amino-carbonyl)pyrrolidin-1-carbonyl]propionamide



The title compound was prepared according to General Procedure E from 2-aminobenzothiazole. ES-MS: cald. For $C_{20}H_{26}N_4O_4S$ (418.17); found 419.4 [M+1].

Example 151

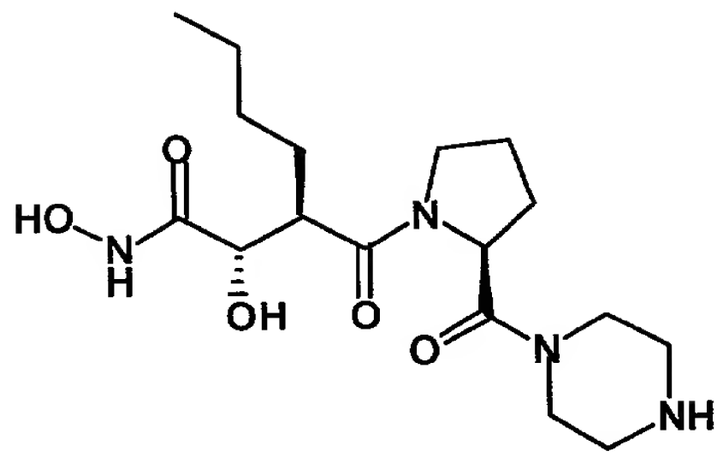
Synthesis of *N*-hydroxy-3-(*R*)-(*n*-butyl)-3-[2-(*S*)-((4-phenylthiazol-2-yl)amino-carbonyl)pyrrolidin-1-carbonyl]propionamide



The title compound was prepared according to General Procedure E from 2-amino-4-phenylthiazole. ES-MS: cald. For $C_{22}H_{28}N_4O_4S$ (444.18); found 445.5 [M+1].

Example 152

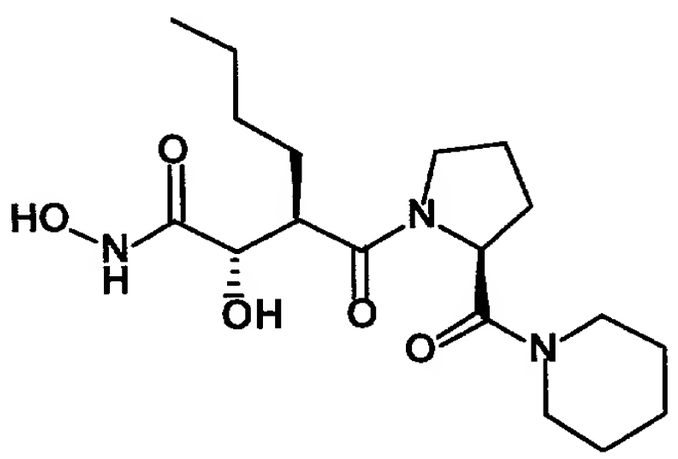
Synthesis of *N*-hydroxy-3-(*R*)-(*n*-butyl)-3-[2-(*S*)-(piperazin-1-ylcarbonyl)pyrrolidin-1-carbonyl]-2-(*S*)-hydroxypropionamide



The title compound was prepared according to General Procedure F from piperazine. ^{1}H NMR (CD_3OD): δ 4.25-4.15 (m, 2H), 4.14 –3.82 (m, 4H), 3.72-3.45 (m, 6H), 3.36-3.29 (m, 1H), 2.46-2.04 (m, 4H), 1.83-1.49 (m, 6H), 1.12 (t, J = 7 Hz). ES-MS: calcd. For $C_{17}H_{30}N_4O_5$ (370.44); found: 371.4 [M+1].

Example 153

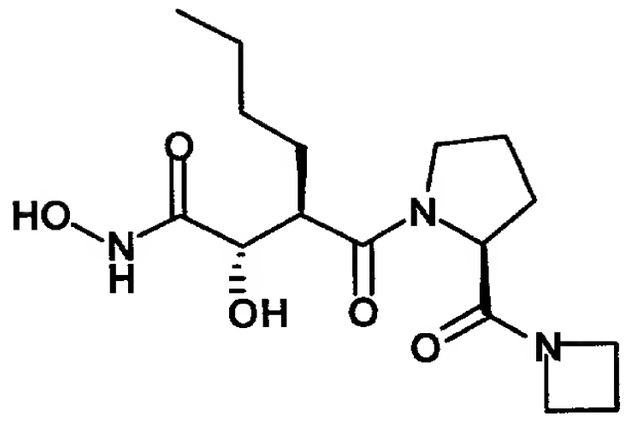
Synthesis of *N*-hydroxy-3-(*R*)-(*n*-butyl)-3-[2-(*S*)-(piperidin-1-ylcarbonyl)pyrrolidin-1-carbonyl]-2-(*S*)-hydroxypropionamide



The title compound was prepared according to General Procedure F from piperidine. ^{1}H NMR ($CDCl_3$): δ 5.07-5.03 (m, 1H), 4.45 (d, J = 2.6 Hz, 1H), 3.97-3.82 (m, 4H), 3.71-3.56 (m, 2H), 3.47-3.40 (m, 1H), 2.37-2.14 (m, 4H), 2.09-1.98 (m, 4H), 1.96-1.61 (m, 4H), 1.59-1.52 (m, 4H), 1.12 (t, J = 7 Hz, 3H). ES-MS: calcd. For $C_{18}H_{31}N_3O_5$ (369.46); found: 370.3 [M+1].

Example 154

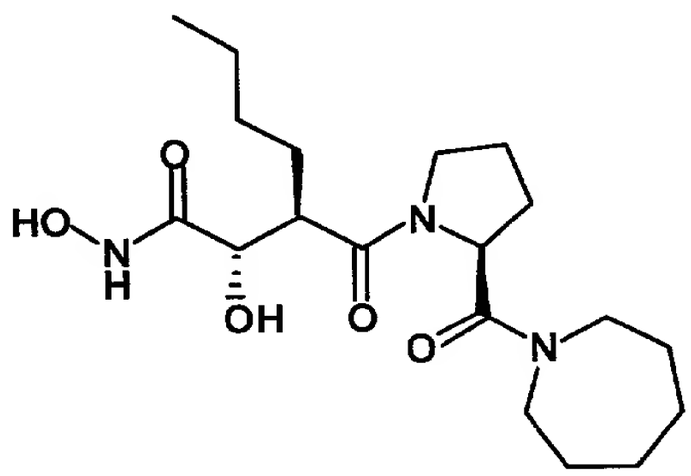
Synthesis of *N*-hydroxy-3-(*R*)-(*n*-butyl)-3-[2-(*S*)-(azetidin-1-ylcarbonyl)pyrrolidin-1-carbonyl]-2-(*S*)-hydroxypropionamide



The title compound was prepared according to General Procedure F from azetidine. ^{1}H NMR ($CDCl_3$): δ 4.67-4.55 (m, 2H), 4.53-4.31 (m, 3H), 4.28-4.16 (m, 1H), 3.94-3.83 (m, 1H), 3.81-3.77 (m, 1H), 3.43-3.38 (m, 1H), 2.55-2.45 (m, 2H), 2.37-2.22 (m, 2H), 2.20-2.07 (m, 2H), 2.05-1.91 (m, 2H), 1.66-1.47 (m, 4H), 1.01 (t, J = 7 Hz, 3H). ES-MS: calcd. For $C_{16}H_{27}N_3O_5$ (341.40); found: 342.3 [M+1].

Example 155

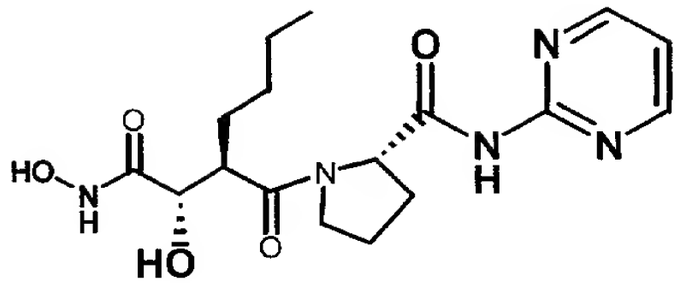
Synthesis of *N*-hydroxy-3-(*R*)-(*n*-butyl)-3-[2-(*S*)-(homopiperazin-1-ylcarbonyl)-pyrrolidin-1-carbonyl]-2-(*S*)-hydroxypropionamide



The title compound was prepared according to General Procedure F from hexamethyleneimine. ^{1}H NMR ($CDCl_3$): δ 5.00-4.96 (m, 1H), 4.44 (d, J = 2.7 Hz, 1H), 3.97-3.82 (m, 2H), 3.79-3.59 (m, 4H), 3.44-3.38 (m, 1H), 2.41-2.30 (m, 2H), 2.19-1.83 (m, 8H), 1.82-1.69 (m, 4H), 1.67-1.50 (m, 4H), 1.10 (t, J = 7 Hz, 3H). ES-MS: calcd. For $C_{19}H_{33}N_3O_5$ (383.48); found: 384.4 [M+1].

Example 156

Synthesis of *N*-hydroxy-3-(*R*)-(*n*-butyl)-3-[2-(*S*)-((pyrimidin-2-yl)amino-carbonyl)pyrrolidin-1-carbonyl]-2-(*S*)-hydroxypropionamide



Step 1

To Cbz-protected-L-proline (20 mmol) in DCM (100 mL) was added thionylchloride (200 mmol) and the solution heated to reflux for 20 min. The reaction was concentrated to dryness and the residue coevaporated two times with DCM. An aliquot (6.7 mmol) in DCM (3 mL) was added to a 0 °C solution of 2-amino-pyrimidine in pyridine (3 mL) and the reaction stirred overnight. The reaction was concentrated, the residue dissolved in ethylacetate and then washed with water, 10 % citric acid, saturated $NaHCO_3$ and brine, then dried (Na_2SO_4) to afford N-Cbz-(2-(*S*)-pyrimidin-2-ylaminocarbonyl)pyrrolidine, which was used without further purification.

Step 2

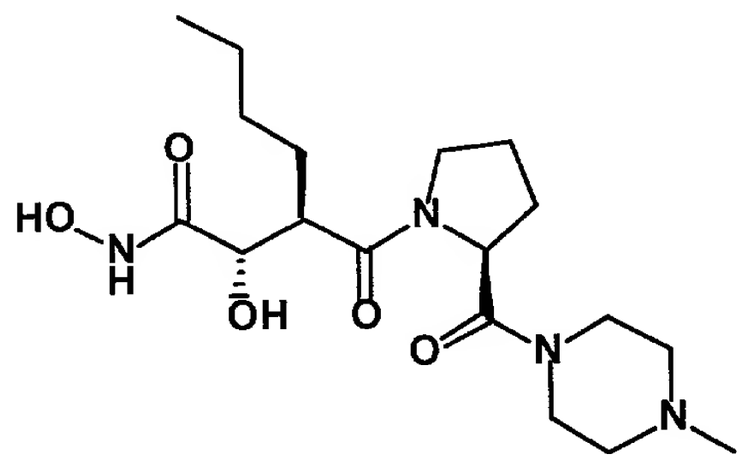
To afford N-Cbz-(2-(*S*)-pyrimidin-2-ylaminocarbonyl)pyrrolidine (5.0 mmol) in HOAc (10 mL) was added 30 % HBr in acetic acid and the solution stirred for 40 min. The reaction was quenched by addition of 100 mL ethylether, and the resulting precipitate collected and recrystalized from MeOH/Et2O to afford 3.5 mmol afford of 2-(*S*)-(pyrimidin-2-ylaminocarbonyl)pyrrolidine hydrobromide salt (70 %).

Step 3

To 2-(*S*)-(pyrimidin-2-ylaminocarbonyl)pyrrolidine hydrobromide (200 μmol) in DMF (2 mL) was added DIEA (500 μmol), compound **G-1**, (General Procedure G, 200 μmol) and solid HATU (200 μmol) and the reaction stirred 4 h. The reaction was cooled to 0 °C, diluted with aqueous 50 % hydroxylamine (600 μL), stirred for 4 h, and then purified via preparative reverse-phase (C18) HPLC to afford the title compound. ^{1}H NMR (DMSO-d6): δ 10.85 (bs, 1H), 8.84 (d, J = 5.0 Hz, 2H), 7.37 (t, J = 5.0 Hz, 1H), 4.98-4.83 (bs, 1H), 4.04-3.95 (m, 2H), 3.78-3.65 (m, 1H), 3.18-3.05 (m, 1H), 2.39-2.25 (m, 4H), 1.57-1.38 (m, 6H), 1.00 (t, J = 6.6 Hz, 3H). ES-MS: calcd. For $C_{17}H_{25}N_5O_5$ (379.4162); found: 380.3 [M+1].

Example 157

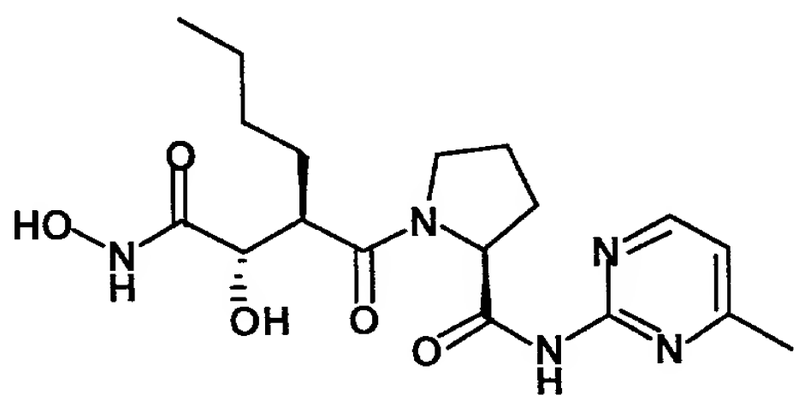
Synthesis of *N*-hydroxy-3-(*R*)-(*n*-butyl)-3-[2-(*S*)-(4-methylpiperazin-1-ylcarbonyl)-pyrrolidin-1-carbonyl]-2-(*S*)-hydroxypropionamide



The title compound was prepared according to General Procedure F from N-methylpiperazine. ^{1}H NMR (CD_3OD): δ 4.24-4.12 (m, 2H), 3.89–3.86 (m, 2H), 3.64-3.51 (m, 4H), 3.35-3.19 (m, 1H), 3.14 (s, 3H), 2.46-2.08 (m, 4H), 1.85-1.53 (m, 6H), 1.11 (t, J = 7 Hz). ES-MS: calcd. For $C_{18}H_{32}N_4O_5$ (384.47); found: 385.3 [M+1].

Example 158

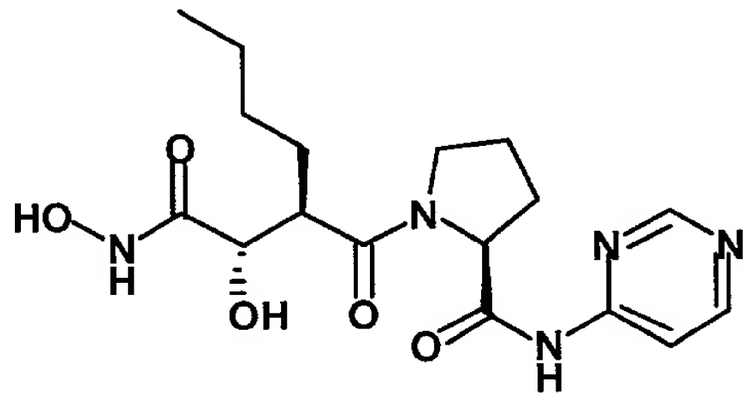
Synthesis of *N*-hydroxy-3-(*R*)-(*n*-butyl)-3-[2-(*S*)-((4-methylpyrimidin-2-yl)amino-carbonyl)pyrrolidin-1-carbonyl]-2-(*S*)-hydroxypropionamide



The title compound was prepared as described in General Procedure F from 4-methyl-2-aminopyrimidine. ^{1}H NMR (DMSO-d6): δ 8.57 (d, J = 5.2 Hz, 1H), 7.16 (d, J = 5.2 Hz, 1H), 4.9 (bs, 1H), 3.93-3.85 (m, 2H), 3.67-3.60 (m, 1H), 3.02-2.90 (m, 1H), 2.50 (s, 3H), 2.3-2.15 (m, 1H), 2.10-1.98 (m, 3H), 1.55-1.28 (m, 6H), 0.904 (t, J = 6.2 Hz, 3H). ES-MS: calcd. For $C_{18}H_{27}N_5O_5$ (393.4431); found: 394.3 [M+1].

Example 159

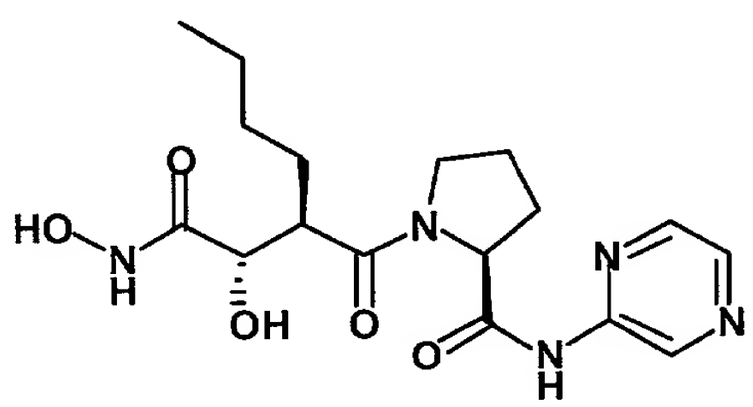
Synthesis of *N*-hydroxy-3-(*R*)-(*n*-butyl)-3-[2-(*S*)-((pyrimidin-4-yl)amino-carbonyl)pyrrolidin-1-carbonyl]-2-(*S*)-hydroxypropionamide



The title compound was prepared as described in General Procedure F from 4-aminopyrimidine. ^{1}H NMR (DMSO-d6): δ 8.91 (d, J = 0.55 Hz, 1H), 8.66 (d, J = 6.1 Hz, 1H), 8.04 (dd, J = 6.1 & 1.1 Hz, 1H), 4.64-4.60 (m, 1H), 3.87-3.75 (m, 1H), 3.61-3.51 (m, 1H), 2.93-2.88 (m, 1H), 2.17-2.05 (m, 1H), 1.98-1.83 (m, 3H), 1.45-1.18 (m, 6H), 0.83 (t, J = 6.3 Hz, 3H). ES-MS: calcd. For $C_{17}H_{25}N_5O_5$ (379.4162); found: 380.1 [M+1].

Example 160

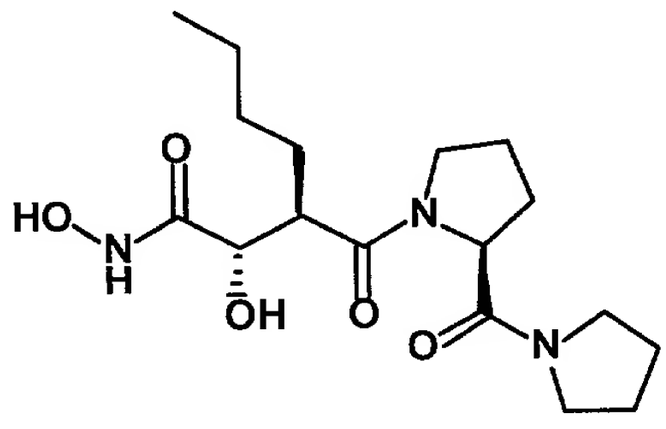
Synthesis of *N*-hydroxy-3-(*R*)-(*n*-butyl)-3-[2-(*S*)-((pyrazin-2-yl)amino-carbonyl)pyrrolidin-1-carbonyl]-2-(*S*)-hydroxypropionamide



The title compound was prepared as described in General Procedure F from aminopyrazine. ^{1}H NMR (DMSO-d6): δ 9.30 (d, J = 1.4 Hz, 1H), 8.41-8.35 (m, 2H), 4.66-4.62 (m, 1H), 3.88-3.76 (m, 2H), 3.60-3.53 (m, 1H), 2.94-2.89 (m, 1H), 2.17-2.11 (m, 1H), 2.00-1.84 (m, 3H), 1.42-1.18 (m, 6H), 0.82 (t, J = 6.6 Hz, 3H). ES-MS: calcd. For $C_{17}H_{25}N_5O_5$ (379.4162); found: 380.4 [M+1].

Example 161

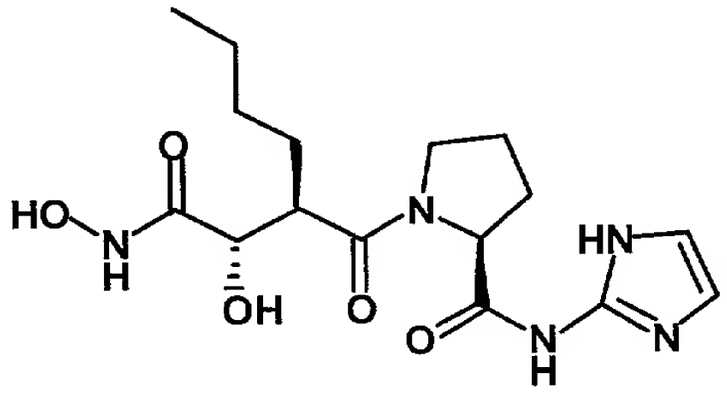
Synthesis of *N*-hydroxy-3-(*R*)-(*n*-butyl)-3-[2-(*S*)-(pyrrolidin-1-ylcarbonyl)pyrrolidin-1-ylcarbonyl]-2-(*S*)-hydroxypropionamide



The title compound was prepared according to General Procedure F from pyrrolidine. ^{1}H NMR ($CDCl_3$): δ 4.83-4.79 (m, 1H), 4.44 (d, J = 2.4 Hz, 1H), 3.96-3.85 (m, 2H), 3.77-3.73 (m, 2H), 3.64-3.56 (m, 2H), 3.42-3.16 (m, 1H), 2.39-2.22 (m, 2H), 2.19-1.96 (m, 8H), 1.66-1.50 (m, 4H), 1.11 (t, J = 7 Hz, 3H). ES-MS: calcd. For $C_{17}H_{29}N_3O_5$ (355.43); found: 356.4 [M+1].

Example 162

Synthesis of *N*-hydroxy-3-(*R*)-(*n*-butyl)-3-[2-(*S*)-((imidazol-2-yl)amino-carbonyl)pyrrolidin-1-carbonyl]-2-(*S*)-hydroxypropionamide



The title compound was prepared as described in General Procedure F from 2-amino-imidazole. ^{1}H NMR (DMSO-d6): δ 7.24 (s, 2H), 4.50-4.46 (m, 1H), 3.83-3.61 (m, 3H), 2.94-2.88 (m, 1H), 2.21-2.11 (m, 1H), 2.05-1.94 (m, 3H), 1.41-1.18 (m, 6H), 0.81 (t, J = 6.0 Hz, 3H). ES-MS: calcd. For $C_{16}H_{25}N_5O_5$ (367.4052); found: 368.4 [M+1].

Formulation Examples

The following are representative pharmaceutical formulations containing a compound of Formula (I).

Example 1

Tablet formulation

The following ingredients are mixed intimately and pressed into single scored tablets.

Ingredient	Quantity per tablet, mg
compound of this invention	400
cornstarch	50
croscarmellose sodium	25
lactose	120
magnesium stearate	5

Example 2

Capsule formulation

The following ingredients are mixed intimately and loaded into a hard-shell gelatin capsule.

Ingredient	Quantity per capsule, mg
compound of this invention	200
lactose, spray-dried	148
magnesium stearate	2

Example 3

Suspension formulation

The following ingredients are mixed to form a suspension for oral administration.

Ingredient	Amount
compound of this invention	1.0 g
fumaric acid	0.5 g
sodium chloride	2.0 g
methyl paraben	0.15 g
propyl paraben	0.05 g

granulated sugar	25.0 g
sorbitol (70% solution)	13.00 g
Veegum K (Vanderbilt Co.)	1.0 g
flavoring	0.035 ml
colorings	0.5 mg
distilled water	q.s. to 100 ml

Example 4

Injectable formulation

The following ingredients are mixed to form an injectable formulation.

Ingredient	Amount
compound of this invention	0.2 mg-20 mg
sodium acetate buffer solution, 0.4 M	2.0 ml
HCl (1N) or NaOH (1N)	q.s. to suitable pH
water (distilled, sterile)	q.s. to 20 ml

Example 5

Suppository formulation

A suppository of total weight 2.5 g is prepared by mixing the compound of the invention with Witepsol® H-15 (triglycerides of saturated vegetable fatty acid; Riches-Nelson, Inc., New York), and has the following composition:

compound of the invention	500 mg
Witepsol® H-15 balance	

Biological Examples

Example 1

Inhibition of peptide deformylase activity

The PDF/FDH coupled assay (Lazennec, C. & Meinnel, T., Anal. Biochem. 224:180-182 (1997)) was used. In this coupled assay, the formate released by PDF from its substrate fMAS is oxidized by the coupling enzyme FDH, reducing one molecule of NAD^+ to NADH, which causes an increase in absorption at 340 nm. All assays were carried out at room temperature in a buffer of 50 mM HEPES, pH 7.2, 10 mM NaCl, 0.2 mg/mL BSA, in half-area 96-well microtiter plates (Corning). The reaction was initiated by adding a mixture of 0.5 Unit/mL FDH, 1 mM NAD^+, and fMAS at the desired concentration. To determine IC_{50} (the concentration needed to inhibit 50% of enzyme activity) values, PDF was pre-incubated for 10 min with varying concentrations of actinonin, and the deformylation reaction was initiated by the addition of reaction mixture containing 4 mM fMAS. The initial reaction velocity, y, was measured as the initial rate of absorption increase at 340 nm using a SpectraMax plate reader (Molecular Devices, Sunnyvale, CA). The inhibitor concentration [In] at which 50% of the enzyme activity is inhibited, IC_{50}, was calculated using the following formula:

$$y = y_o/(1 + [In]/IC_{50})$$

where y_o is the reaction velocity in the absence of inhibitor. The IC_{50} was calculated based on a nonlinear least-square regression fit using a commercial software package (DeltaGraph 4.0, Deltapoint, Inc., Chicago, Il).

Using this assay, the IC_{50} of various compounds were determined. The IC_{50} for the various compounds was determined against deformylase enzyme containing nickel or zinc as the metal ion. The compound tested had an IC50 of less than 2 μM against deformylase enzyme containing nickel as the metal ion and less than 9 μM against deformylase enzyme containing zinc as the metal ion

Example 2

Assay for testing antimicrobial activity

Minimum inhibitory concentrations (MICs) were determined using the microdilution method in 96-well format plates. Compounds were suspended in DMSO at 5 or 10 mg/ml and stored at 4°C until used. They were diluted in Mueller-Hinton Broth (MHB) or Trypticase Soy Broth (TSB) and used for MIC determination.

The range of concentrations tested was 64-0.0625 μg/ml final concentration using a two-fold dilution system.

The inoculum was prepared from cells grown on Trypticase Soy Agar (TSA) and incubated overnight at 35 °C, 5 to 10 colonies were used to inoculate MHB or TSB broths, and the culture was incubated overnight at 35°C. The overnight culture was diluted 1:10, incubated for one hour at 35°C, diluted to the appropriate inoculum size and applied to the wells containing broth and test compound. Inoculum sizes were $2x10^4$ CFU/ml.

Plates were incubated at 35°C for 48 hours and MIC were recorded after 18 hours of incubation for bacteria. MIC was defined as the lowest concentration of compound that does not produce visible growth after incubation.

Minimum inhibitory concentrations for various compounds against *H. influenza* and *S. aureus* was approximately 64 μg/mL or less.

Minimum inhibitory concentrations for certain compounds of the Invention against *S.* aureus, S. epidermidis, E. faecium, S. pneumoniae, H. influenzae, H. influenzae acr, M. catarrhalis, E. coli and E. coli acr was approximately 64 μg/mL or less.

Example 3

Demonstration of Selective Inhibition of PDF Compared to MMP-7 (Matrilysin)

As noted previously, inhibitors which are selective for peptidyl deformylase over matrix metalloproteinases are desirable in order to avoid side effects.

In order to test the compounds of the invention for possible inhibitory effects on matrix metalloproteinases, the following assay for MMP-7 (matrilysin) was used.

MMP-7 (Matrilysin) Assay:

Matrilysin activity is assayed using a thio-peptide (Pro-Leu-Gly-S-Leu-Leu-Gly) as substrate. Upon enzyme hydrolysis, the thiolate is released as a product. The thiolate thus generated reacts with DTNB (dithionitrobenzene), giving rise to a yellow color which is monitored at 405 nm. The assay is carried out at room temperature; the assay buffer contains 50 mM Tricine, pH 7.5, 0.2 M NaCl, 10 mM $CaCl_2$, and 0.05% Brij, in a half-area 96-well microtiter plate. The reaction is initiated by adding a mixture of 200 μM DTNB and 100 μM thiopeptide in buffer. To determine IC_{50} (the concentration needed to inhibit 50% of enzyme activity) values, MMP-7 was preincubated for 10 minutes with varying concentrations of compounds, and the

hydrolysis initiated by the addition of reaction mixture containing thiopeptide and DTNB. The reaction rate was recorded as the absorbance increase in OD_{405} over 30 minutes using a SpectraMax plate reader (Molecular Devices, Sunnyvale, CA). The inhibitor concentration [In] at which 50% of the enzyme activity is inhibited, IC_{50}, was calculated using the following formula:

$$y = y_o/(1 + [In]/IC_{50})$$

where y_o is the reaction velocity in the absence of inhibitor. Solving this equation for IC_{50} at the [In] when $y = y_o/2$ yields IC_{50}.

Using this assay, the IC_{50} of various compounds were determined. The compounds of the Invention tested were at least approximately 800 times more select for PDF than MMP-7. Similar selectivity of the compounds for peptidyl deformylase over MMP-1, MMP-2, MMP-3, MMP-9, MMP-13, MT-MMP-1, and tissue necrosis factor converting enzyme was observed. Similar selectivity was also observed over other metalloproteinases such as angiotensin converting enzyme.

Example 4

Discontinuous PDF Assay

The gene for PDF was cloned from *S. aureus* and *E. coli* by PCR amplification. The PDF proteins were overexpressed in E. coli. The native Fe^{2+}-containing PDF or its more stable surrogate Ni^{2+}-containing PDF were prepared according to Wagner et al. (1998) *Biochemical & Biophysical Research Communications* **246:**342-6. Both enzymes have similar activity as reported in the literature. Discontinuous assay is carried out in a buffer of 10 mM NaCl and 50 mM HEPES, pH 7.2. Typically, 2 nM of PDF was incubated with inhibitor for 30 minutes prior to the addition of 4 mM fMAS substrate. The deformylation proceeded at room temperature for 30 minute. The enzyme activity is directly proportional to the amount of formate released, which can be quantified by monitoring the absorbance increase at 340 nm after the addition of 1 mM of NAD^+ and 0.5 U/ml of formate dehydrogenase.

Example 5

Mouse septicemia model for determining in vivo efficacy

CD1 female out-bred mice (Charles River Laboratories) weighing 18-22 grams each were injected intraperitoneally with 0.5 ml of a suspension containing $5x10^7$ cfu of *S. aureus* (Smith strain) in 7% hog gastric mucosa (mucin). The mice

were treated, either subcutaneously (SC), intravenously (IV) or orally (PO), 1hr and 5hr after infection. Six groups of six mice each were given different dosage levels representing two-fold dilutions of each compound (range of 100mg/kg – 0.1 mg/kg). Vancomycin was used as the control antibiotic and was administered SC. Compounds were formulated in PBS and untreated controls were dosed with vehicle alone.

Deaths in each group were monitored daily for 6 days and cumulative mortality was used to determine the 50% protective doses (PD_{50}), which were calculated using the method of Reed and Muench.

The foregoing invention has been described in some detail by way of illustration and example, for purposes of clarity and understanding. It will be obvious to one of skill in the art that changes and modifications may be practiced within the scope of the appended claims. Therefore, it is to be understood that the above description is intended to be illustrative and not restrictive. The scope of the invention should, therefore, be determined not with reference to the above description, but should instead be determined with reference to the following appended claims, along with the full scope of equivalents to which such claims are entitled.

All patents, patent applications and publications cited in this application are hereby incorporated by reference in their entirety for all purposes to the same extent as if each individual patent, patent application or publication were so individually denoted.